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(20)

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BRIEF SUMMARY—(Please consult full package insert, enclosed in every package, before using Regonol)

INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg/kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, reoxygenation has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

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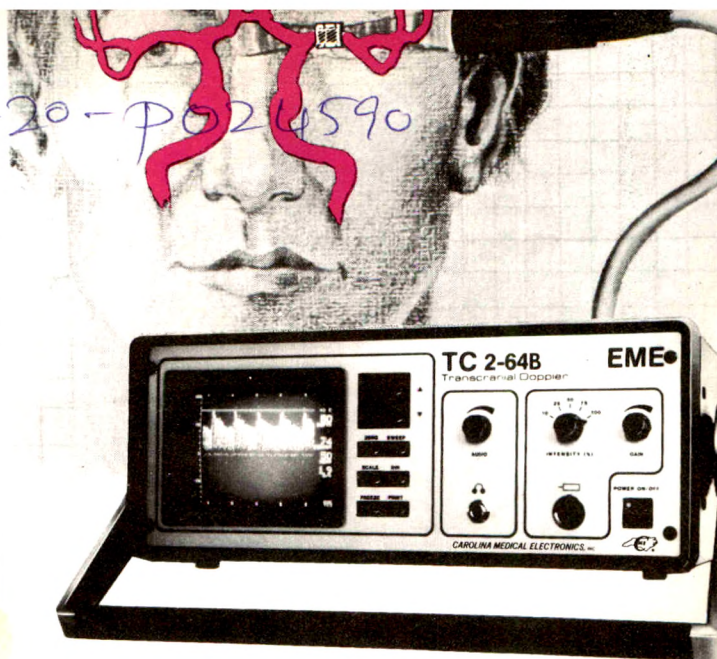
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2. Ravin MB. Pyridostigmine as an antagonist of d-tubocurarine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.



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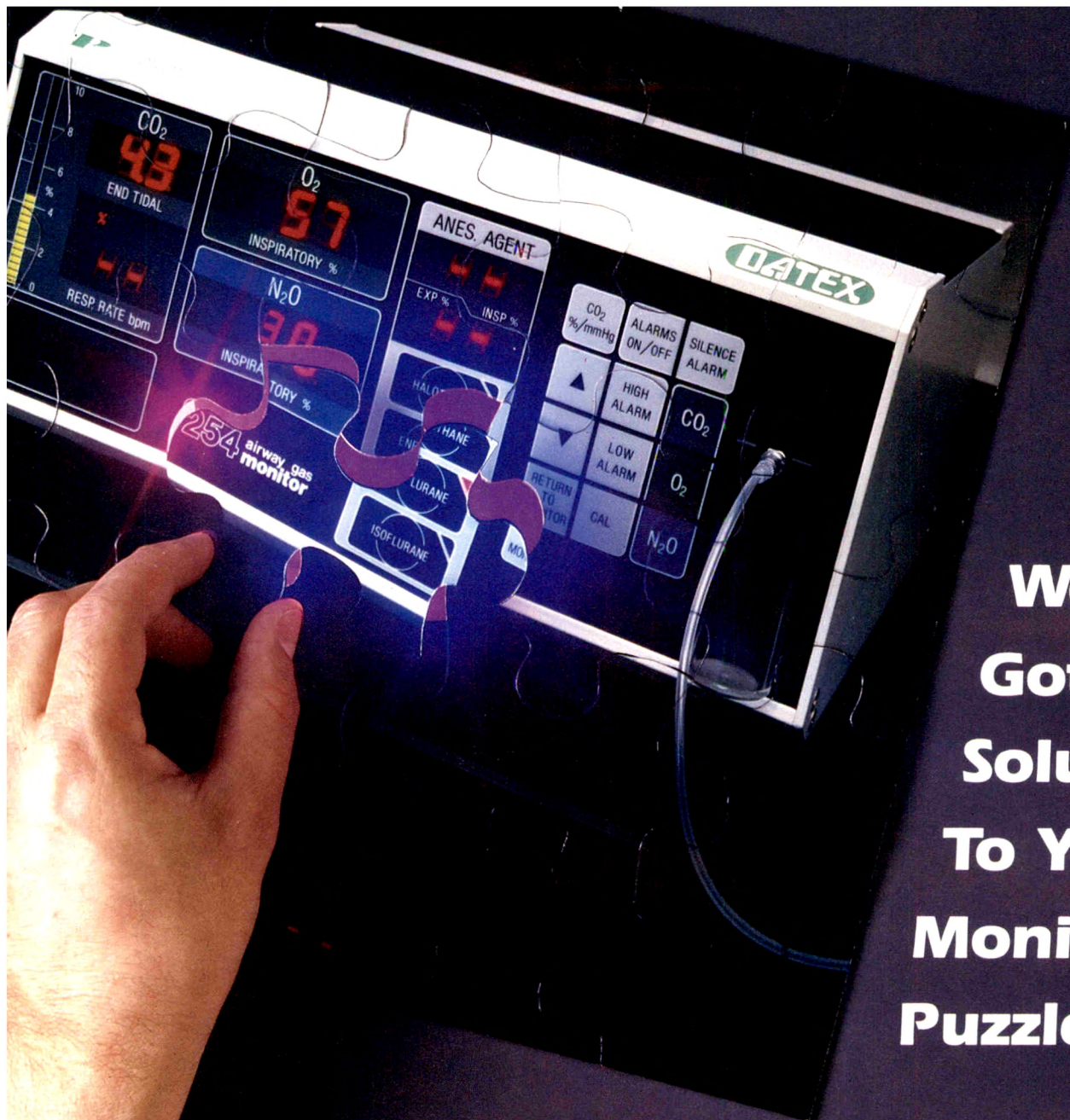
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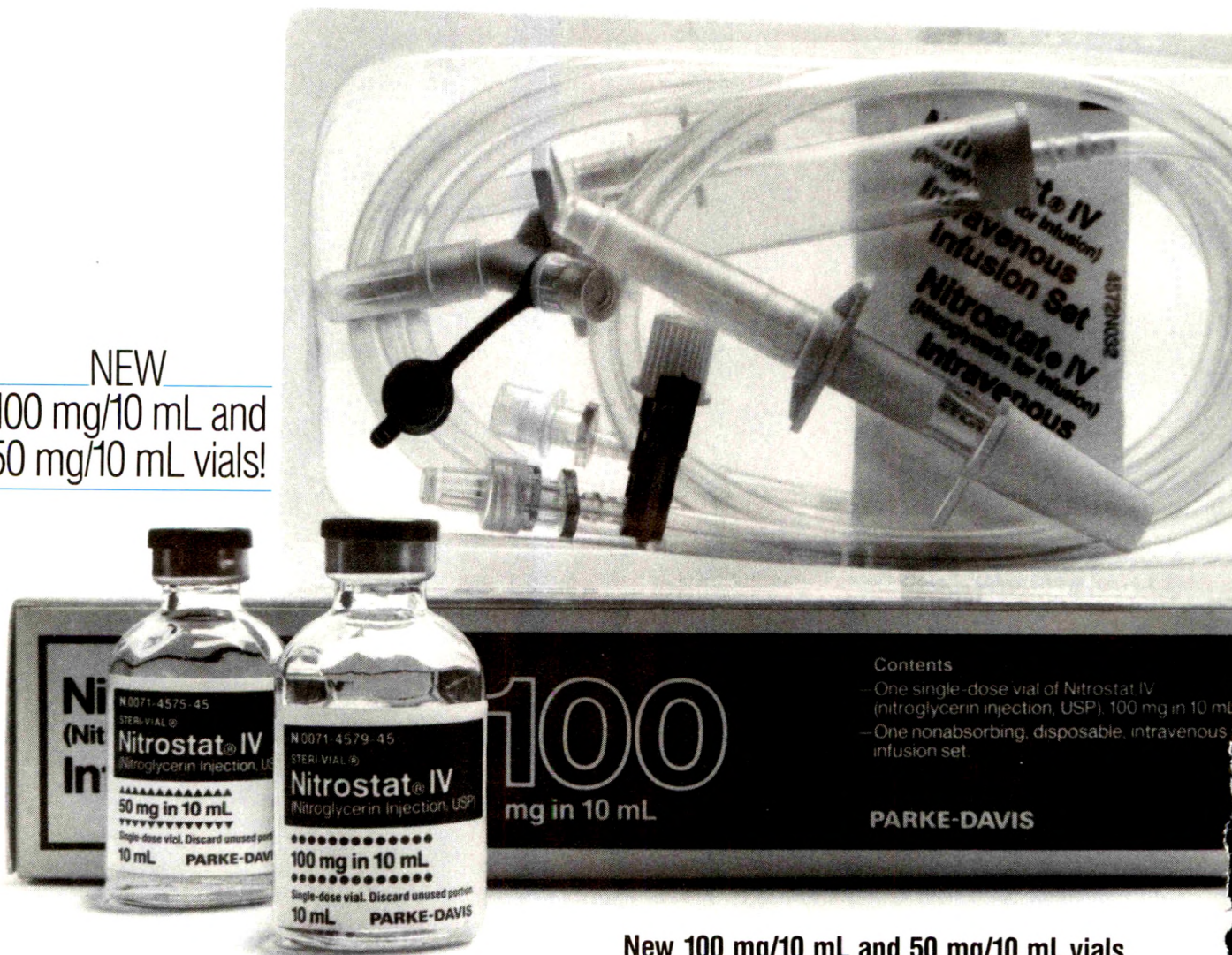
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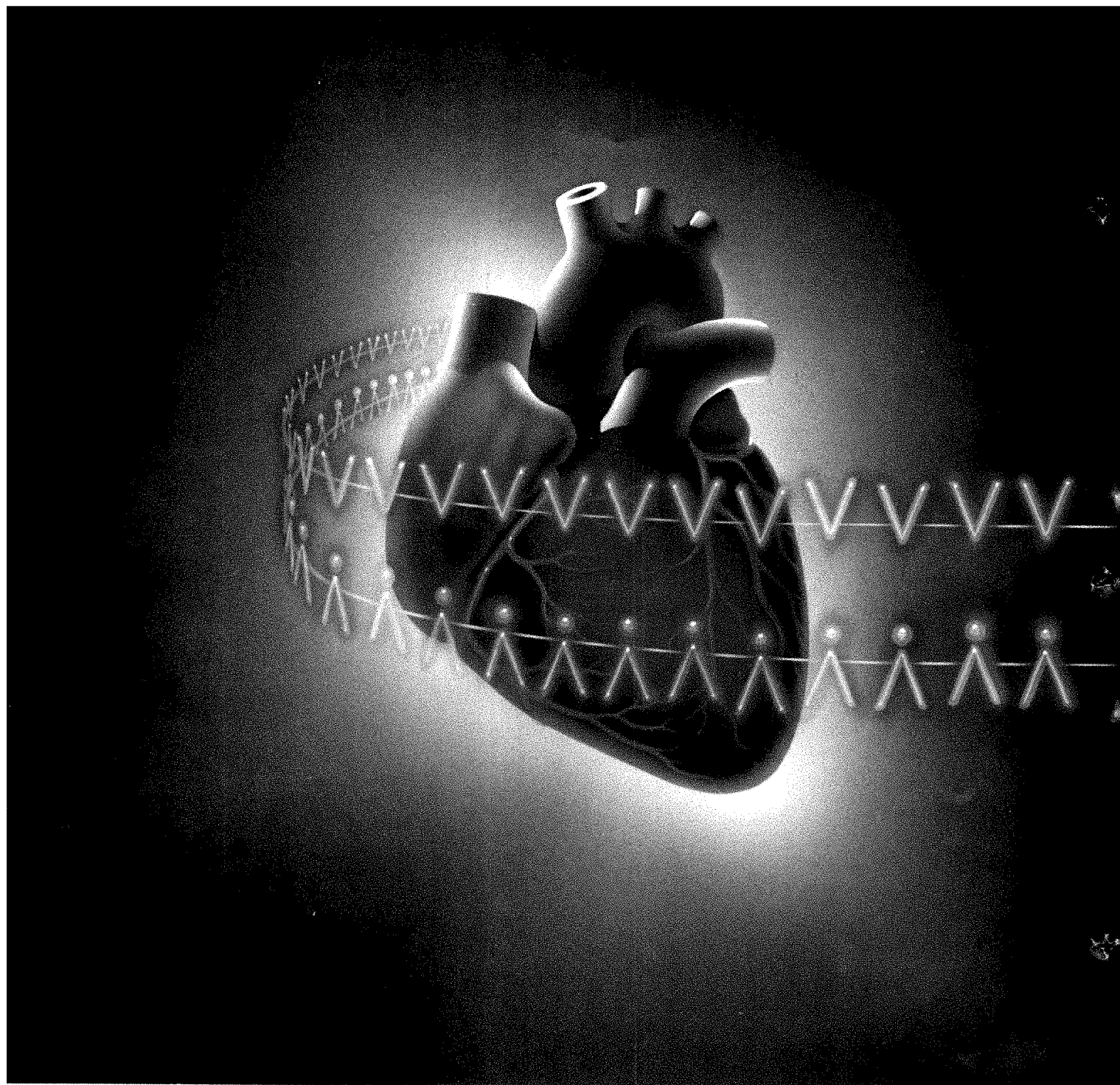
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An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to $1/4$ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 $\mu\text{g}/\text{kg}$, 2) administration of a full paralyzing dose of a neuromuscular blocking agent

following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 $\mu\text{g}/\text{kg}$) titrated by slow intravenous infusion, or 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 $\mu\text{g}/\text{kg}$). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion

**THE PRIMARY ANESTHETIC
THAT KEEPS PATIENTS
ON TRACK**

SUFENTA[®] (sufentanil citrate) Injection

Predictable control for longer, more stressful procedures

PROVIDES smooth induction¹

**BLUNTS hemodynamic response to intubation
and surgical stimulation²**

**REDUCES need for vasoactive drugs in
the intraoperative and postoperative periods¹**

**RESULTS in lower postoperative morbidity after
aortic surgery compared with isoflurane³**
(in a randomized study comparing sufentanil and isoflurane)

CONVENIENT: Fewer ampoules to open

of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD₅₀ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm

Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD₅₀ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD₅₀s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).



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U.S. Patent No. 3,998,834
7618504-M
January 1986, March 1986
JPI 710

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Enlon[®]
(edrophonium chloride
injection, USP)

**A rapid-acting
neuromuscular reversal agent**

**From the developers of
Ethrane[®] (enflurane) and Forane[®] (isoflurane)**

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60-second reversal of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.^{1,2}
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.^{1,2*}
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 µg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 µg/kg).^{1,2}
- **May be the preferred reversal agent for atracurium and vecuronium**
“...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade.”³
“Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug.”⁴

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. *Anesthesiology* 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. *Anesthesiology* 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. *Br J Anaesth* 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. *Br J Anaesth* 54:375-385, 1982.

Please see use information on next page.

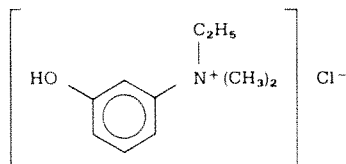
Anaquest



Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle, intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

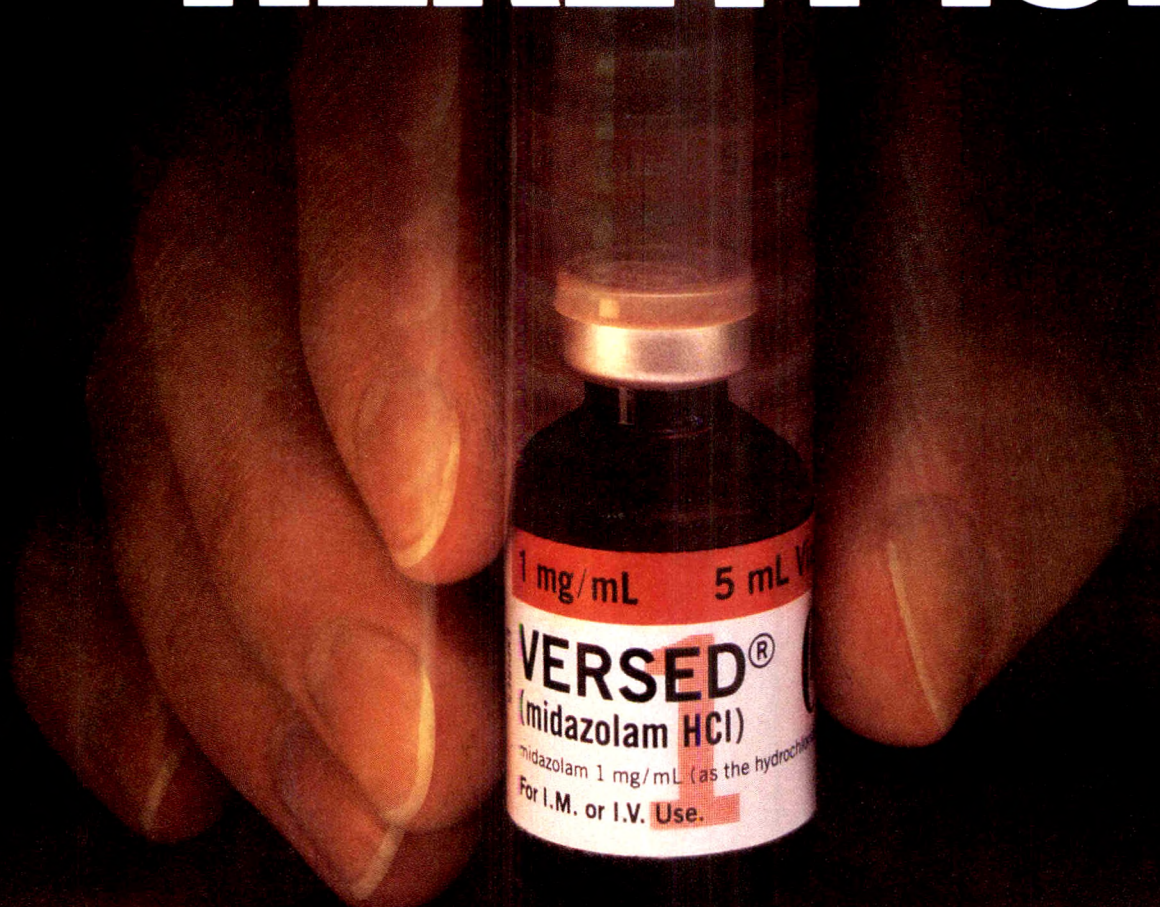
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Revised 10-85

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for your convenience.

New strength:
1 mg/mL
in 2-mL, 5-mL and
10-mL vials
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Also available:
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and 10-mL vials
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VERSED
brand of
midazolam HCl
equivalent to 1 mg/mL and 5 mg/mL
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**IN SHORT SURGICAL
PROCEDURES,
AN OPTIMAL OPIOID
ANESTHETIC FOR**

MOMENT-TO- MOMENT CONTROL

RAPID ONSET OF ACTION

for prompt control of hemodynamic response
to surgical stimulation*

SHORT DURATION OF ANALGESIC ACTION

permits titrating to patient response

PROMPT RECOVERY

in short-stay procedures†

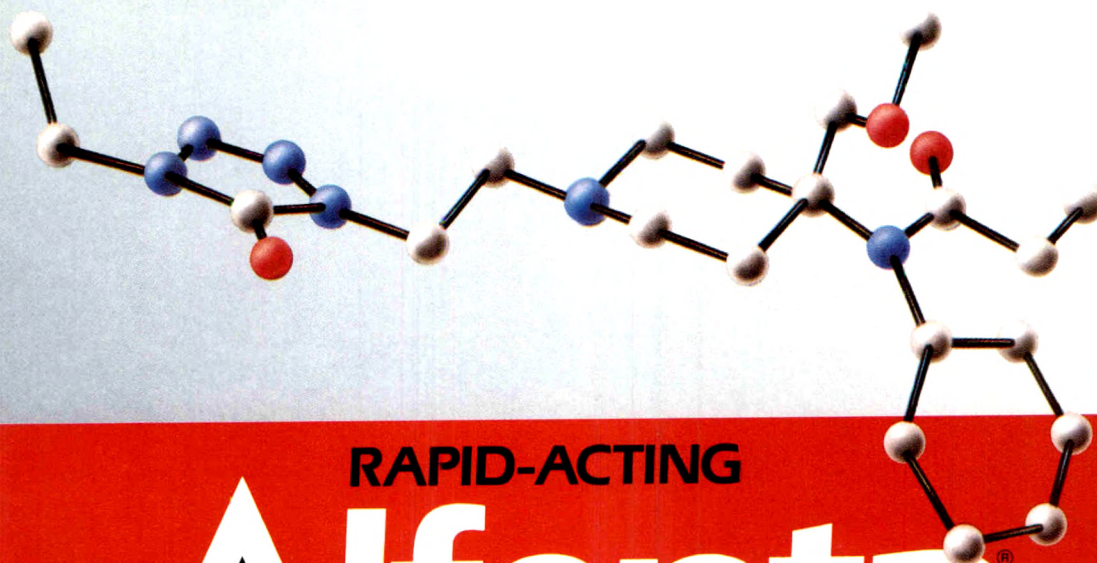
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RAPID-ACTING

Alfenta

(alfentanil HCl) Injection II

**A PHARMACOKINETIC PROFILE
THAT PERMITS FLEXIBILITY OF
DOSING TECHNIQUE**

**BOLUS/INCREMENTAL
ADMINISTRATION**

for short procedures lasting up to 30 minutes
in spontaneously breathing patients, or for procedures
lasting 30 to 60 minutes in intubated patients

**CONTINUOUS
INFUSION**

for procedures lasting more than 45 minutes
in intubated patients

*As with other opioids, hypotension and bradycardia have been reported.

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

*See following page for brief summary of Prescribing Information.

RAPID-ACTING

Alfenta®

(alfentanil HCl) Injection

AN OPTIMAL OPIOID ANESTHETIC FOR MOMENT-TO-MOMENT CONTROL

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION, OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO₂. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported, therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N = 785) %	Fentanyl (N = 243) %	Thiopental Sodium (N = 66) %	Enflurane (N = 55) %	Halothane (N = 18) %	Saline Placebo* (N = 18) %
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD₅₀ of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

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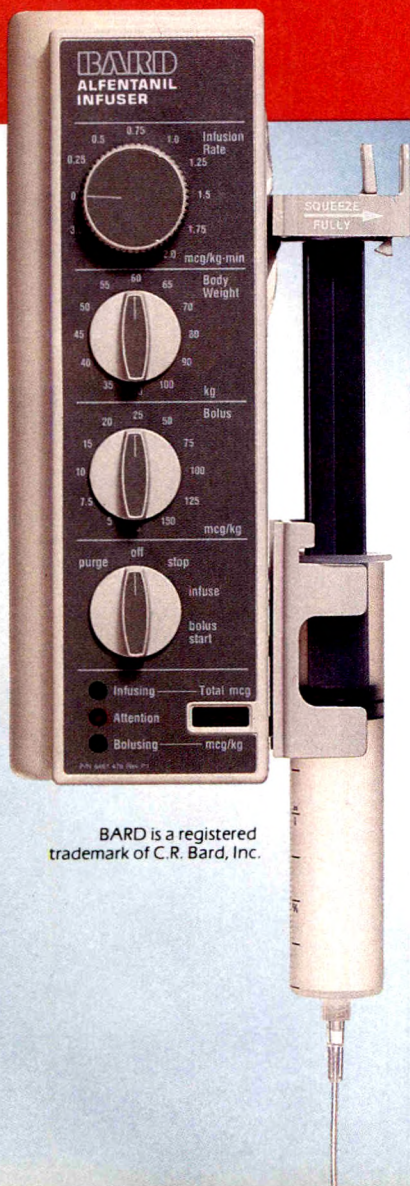
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6% Hetastarch in 0.9% Sodium Chloride

Injection

CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of Hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time. Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of Hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of Hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by Hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since Hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children. The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which Hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7mg%) have been reported in 2 out of 20 normal subjects who received multiple Hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering Hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of Hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see **ADVERSE REACTIONS**). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED

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The Influence of Acidosis on the Distribution of Lidocaine and Bupivacaine into the Myocardium and Brain of the Sheep

C. Nancarrow, FFARACS, W. B. Runciman, FFARACS, PhD, L. E. Mather, PhD, FFARACS, R. N. Upton, BSc, and J. L. Plummer, PhD

NANCARROW C, RUNCIMAN WB, MATHER LE, UPTON RN, PLUMMER JL. The influence of acidosis on the distribution of lidocaine and bupivacaine into the myocardium and brain of the sheep. *Anesth Analg* 1987;66:925-35.

To test the hypothesis that acidosis can increase the toxicity of bupivacaine more than that of lidocaine by increasing the distribution into the brain, myocardium, or both, studies were performed to measure the in vivo tissue:blood partition coefficients during continuous steady state intravenous infusions of these agents in anesthetized sheep during normal acid-base status and during combined respiratory-metabolic acidosis. Acidosis decreased the partition coefficient of both

agents into the myocardium and that of bupivacaine into the brain but did not systematically change that of either agent into skeletal muscle or fat. Total body and hepatic drug clearances were not affected systematically, but plasma binding of both agents was decreased. Thus predictions based on the pH partition hypothesis about the effects of acidosis on myocardial:blood partition coefficients being a basis for explaining the relative toxicity of these agents were not supported.

Key Words: ANESTHETICS, LOCAL—lidocaine, bupivacaine. ACID-BASE EQUILIBRIUM—acidosis. SOLUBILITY—partition coefficients. TOXICITY—local anesthetic.

Recent studies have indicated that bupivacaine can disturb cardiac electrophysiology to a greater extent than lidocaine and that this is the basis for its having a greater potential to produce cardiotoxicity (1-4). Evidence from experiments performed both in vitro (5) and in vivo (1,6) indicates that the cardiotoxicity of bupivacaine relative to that of lidocaine is exacerbated by acidosis and hypoxia.

Acidosis could increase the distribution of both these local anesthetic agents into the heart and brain by at least two mechanisms. First, by increasing the fraction ionized of these basic drugs, acidosis may cause their "ion-trapping" into tissue; the effect would be greater for bupivacaine (pKa 8.1) than lidocaine (pKa 7.9) (7). Second, acidosis may decrease the degree of binding of both drugs in blood (8) and allow greater uptake into tissue; the effect would be relatively greater for bupivacaine than lidocaine because of its higher fraction bound. In order to examine the hypothesis that

the relatively greater toxicity of bupivacaine in acidosis is due to relatively greater uptake into the myocardium or brain, studies were designed to examine the influence of acidosis on tissue:blood partition coefficients of both bupivacaine and lidocaine for myocardium and brain and to compare the binding of both drugs in normal and acidotic blood. In these studies, it was not planned to examine the influence on tissue partition coefficients of coexistent conditions such as hypoxia, hyperkalemia, or anemia.

Methods

Animal Preparation

These studies were approved by the appropriate institutional ethics review committee. Eight Merino ewes were prepared for studies with multiple intravascular cannulae. The reasons for the choice of species and the physiologic profile of the experimental preparation have been presented in detail elsewhere (9). Only details relevant to the present study are described here.

To allow placement of cannulae, general anesthesia was induced with sodium thiopental (20 mg/kg) and, after endotracheal intubation, the animals were ventilated with 40% oxygen and 1-1.5% halothane (bal-

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ance nitrogen). The right carotid artery and jugular vein were exposed, and cannulae were placed using the Seldinger method and with the guidance of x-ray image intensification. Three straight 7-F braided cannulae were inserted via the carotid artery with their tips lying in the ascending aorta approximately 2 cm above the aortic valve. Venous cannulae were placed (a) in the coronary sinus for measurement of myocardial effluent drug concentrations; (b) in the right atrium, one for injection of cold dextrose during measurement of cardiac output and another for infusion of bromosulfthalein (BSP); (c) in the inferior vena cava for local anesthetic infusion; and (d) in the hepatic vein for measurement of hepatic blood flow and hepatic local anesthetic extraction ratio. In addition, a Swan-Ganz catheter was positioned in the main pulmonary artery for measurement of cardiac output by thermodilution. Catheters were secured and maintained as previously described (9). In addition, to obtain representative cerebral effluent blood, a 3-F polyethylene catheter was placed in the sagittal sinus via a frontal incision and a trephine hole in the parietal bone (10). The animals were allowed to recover from these procedures for a period of 3 days prior to the study day. It had been previously shown that the animals would remain in good health with normal cardiovascular homeostatic mechanisms after these procedures (9).

Experimental Design

The principal objective of this study was to obtain concurrent samples of arterial blood, myocardium, and brain to determine the influence of acidosis on myocardial/blood and brain/blood partition coefficients. In addition, concurrent samples of skeletal muscle and fat were obtained from most animals, and samples of hepatic venous blood were obtained from some animals. These required that animals be anesthetized. This was done as described above.

Measurement of partition coefficient between blood and tissue required steady-state blood concentrations of local anesthetic. A two-stage IV infusion of lidocaine HCl or bupivacaine HCl was performed in each of four animals at average loading rates of 13.3 and 2.9 mg/min, respectively, and average maintenance rates of 5.6 and 1.5 mg/min, respectively. These rates were chosen in order to achieve blood concentrations of lidocaine approximately four times those of bupivacaine. Exact infusion rates achieved for each animal were determined by using precalibrated syringes and a Harvard infusion pump.

Hemodynamic Measurements

Throughout the study period, hemodynamic measurements were performed every 10 min using previously described methods (9). Cardiac output was determined by thermodilution; mean arterial blood pressure was determined by a calibrated aneroid gauge connected to one of the aortic cannulae. Hepatic blood flow was determined at steady state from the ratio of the BSP infusion rate (3.7 mg/min) to the arteriohepatic venous BSP concentration differences (9,11).

Thoracotomy

After the drug and BSP infusions had been started, a left lateral thoracotomy was performed at the level of the 5th intercostal space, and the surface of the left ventricle and atrium were exposed by incising the pericardium. At this time, the hemi-azygos vein, which drains into the coronary sinus in the sheep (12), was ligated in order to prevent the mixing of systemic venous blood with myocardial venous blood. In this way the blood samples obtained from the catheter placed in the coronary sinus reflected true "myocardial effluent" blood. This had been validated previously (13).

Maintenance of Normal Acid-Base Status

Throughout the study period, acid-base status of the animals was monitored. End-tidal CO₂ concentrations were measured with an infrared CO₂ analyzer (Datex Instrumentarium Corp, Finland). Using a Bain system, adjustments of fresh gas flow and minute ventilation were made in response to the measured CO₂ concentrations in order to keep the end-tidal CO₂ concentration at 4-4.5%. Blood gases and pH determinations were performed approximately every 10 min (Model 813 pH/blood gas analyzer, Instrumentation Laboratories, Lexington, MA). In addition, arterial blood lactate concentrations were measured every 10 min. Over the fourth experimental period, approximately 200 ml blood was sampled; this was replaced with double volume of intravenous crystalloid solution.

Biopsy Techniques

Biopsies of myocardium and brain were taken *after* it had been established that there was a steady state of local anesthetic arterial blood concentrations and that normal acid-base conditions and stable cardiac output had existed for at least 1 hr. Under direct vision,

Table 1. Acid-Base Status of Animals Receiving Infusions to Produce Arterial Steady State Blood Concentrations of Either Lidocaine or Bupivacaine during Control and Acidotic Periods

Sheep	Arterial pH		Coronary sinus pH		Sagittal sinus pH		Arterial lactate concentration (mmol/L)	
	Control	Acidosis	Control	Acidosis	Control	Acidosis	Control	Acidosis
Lidocaine-treated group								
A	7.51	7.08	7.44	7.03	7.41	6.98	4.67	15.26
							5.45	14.30
B	7.37	7.11	7.32	7.06	7.30	7.07	4.53	14.57
							5.48	13.96
C	7.25	7.04	7.20	6.98	7.18	6.94	3.79	10.65
							3.70	10.91
D	7.50	7.17	7.42	7.12	7.39	7.11	1.60	12.56
							1.59	12.28
Bupivacaine-treated group								
E	7.35	7.00	7.30	6.98	7.26	6.95	3.78	14.80
							4.89	16.49
F	7.35	6.94	7.29	6.88	NA	NA	3.95	13.98
							3.93	15.00
G	7.27	6.96	7.24	6.92	7.21	6.94	4.39	15.06
							4.59	14.40
H	7.41	7.11	7.33	7.05	7.32	7.04	2.64	15.18
							2.54	14.03

small (50–100 mg) surface biopsies were taken of both the left ventricle and left atrium. Care was taken to avoid major coronary vessels, and any small vessels that were damaged were ligated to prevent further bleeding. Subsequent biopsies were removed from areas of myocardium at least 1 cm apart and which appeared to have normal tissue perfusion. Small (50–75 mg) cerebral cortical biopsies were taken during both the control and acidotic periods. The previously made trephine hole was enlarged using bone forceps, and the dura was removed in order to expose the cerebral cortex to be biopsied. Biopsy samples of skeletal muscle and fat (approx 100 mg) were removed from an incision in the femoral triangle. Care was taken to avoid major vessels; any small vessels that were damaged were diathermied to prevent further bleeding. Subsequent biopsies were removed from areas at least 1 cm apart and which appeared to have normal tissue perfusion. All biopsy samples were immediately blotted to remove blood from the sample and then frozen in liquid nitrogen. Samples were stored frozen for later analysis of tissue drug concentration. Arterial blood samples were taken within 1 min of the tissue biopsies in order to determine tissue/blood partition coefficients.

Induction of Acidosis

A metabolic acidosis was induced by the passage of a pulsed (50 Hz) DC current of 25–100 mA along the

neuraxis between electrodes placed at the lip and anal areas of the anesthetized sheep (14). This produced a controllable, marked skeletal muscular tonicity accompanied by markedly increased lactic acid production. In this way, the metabolic component of the acidotic state was induced. Concurrent respiratory acidosis was allowed to develop by maintaining relatively constant ventilation and fresh gas flow in the presence of a profound increase in CO₂ production. During overt local anesthetic toxicity, both skeletal muscular hyperactivity (during seizures) and hypoventilation (due to upper airway obstruction) may occur. Thus the procedure employed closely simulated the clinical situation.

The development of acidemia was monitored with repeated end-tidal CO₂ analysis; arterial, coronary sinus, and sagittal sinus pH measurements; and arterial lactate determinations. Once acidosis had been established for 20 min, further myocardial and brain biopsies were taken over 10 min using the technique described above.

Pharmacokinetic Calculations

Partition coefficients for each animal at each stage of the study were determined at steady state by dividing the mean of arterial blood drug concentrations during each period by the mean of the respective tissue drug concentrations during each period. Total body drug clearance was determined from the ratio of infusion

Table 2. Arterial Blood and Tissue Drug Concentrations ($\mu\text{g/ml}$ or $\mu\text{g/gm}$) of Animals Receiving Infusions of either Lidocaine or Bupivacaine during both Control and Acidotic Periods

Sheep	Drug dose rate (mg/min)	Arterial concentration		Left ventricular concentration	
		Control	Acidosis	Control	Acidosis
Lidocaine-treated group					
A	5.47	4.0 ± 0.3 n = 4	5.7 ± 0.1 n = 4	11.9 ± 1.8 n = 3	14.3 ± 14.1 n = 2*
B	5.45	5.0 ± 0.2 n = 4	5.7 ± 0.1 n = 5	9.5 ± 1.0 n = 3	9.8 ± 0.3 n = 3
C	5.91	2.9 ± 0.2 n = 4	2.6 ± 0.1 n = 4	8.1 ± 0.3 n = 3	5.2 ± 0.2 n = 6
D	5.58	4.0 ± 0.2 n = 4	3.7 ± 0.2 n = 5	12.7 ± 1.2 n = 4	9.7 ± 0.9 n = 8
Bupivacaine-treated group					
E	1.62	1.2 ± 0.1 n = 4	2.3 ± 0.2 n = 4	4.5 ± 4.4 n = 2*	4.9 ± 1.2 n = 4
F	1.56	1.4 ± 0.02 n = 4	1.4 ± 0.1 n = 5	2.6 ± 0.5 n = 5	2.3 ± 0.3 n = 6
G	1.21	0.68 ± 0.04 n = 4	0.71 ± 0.05 n = 5	1.8 ± 0.5 n = 4	1.0 ± 0.2 n = 7
H	1.81	1.5 ± 0.1 n = 4	1.5 ± 0.3 n = 5	13.1 ± 1.2 n = 4	6.3 ± 1.5 n = 8

Arterial blood and tissue samples were taken for determinations of drug concentrations during the last 20 min of each period.

*Where $n = 2$ actual values are given.

rate to mean steady state arterial blood concentration. Hepatic clearance was determined from the product of hepatic blood flow and hepatic drug extraction ratio at steady state. Hepatic drug flux was calculated from the product of hepatic blood flow and arteriohepatic venous drug concentration difference at steady state.

Determination of Lidocaine and Bupivacaine Binding in Blood and Plasma. Phosphate buffer (0.067 M) was prepared and the pH adjusted to 7.4 or 7.0 by the addition of NaOH or HCl as necessary. Buffer solutions at each pH were prepared containing lidocaine HCl, 1, 0.5, 0.25, 0.125, 0.025, and 0.005 mg/ml, or containing bupivacaine HCl, 0.12, 0.06, 0.03, 0.015, 0.0025, and 0.000525 mg/ml. These concentrations were calculated to produce whole blood concentrations at equilibrium encompassing the range encountered during local anesthetic toxicity.

Binding studies were performed on blood and plasma collected from three sheep not previously exposed to any drugs. Blood was handled at all stages using sterile technique and was collected from the jugular vein into several 50-ml plastic syringes (Terumo, Melbourne, Australia) which were wet with heparin solution (1000 IU/ml) (CSL, Melbourne, Australia). Blood was transferred into 10-ml plastic tubes containing lithium heparin. One half of the blood was then used for preparation of plasma by centrifugation at 3000 rpm for 10 min which was then pooled in 20-

ml aliquots into sealed glass containers. The remaining blood was also pooled into similar containers containing an additional 300 IU heparin (1000 IU/ml), then gently mixed by manual rotation. Subsequently, both blood and plasma were stored at 4°C until used within 36 hr of collection. Hemoglobin, hematocrit, total protein, and albumin concentrations were measured in blood from each sheep.

Equilibrium dialysis was performed in three compartment cells made of Delrin (DuPont, de Nemours) at 39°C (the normal core temperature of the sheep), as described by La Rosa et al. (15,16). The central chamber was used for buffer containing lidocaine or bupivacaine; blood and plasma were placed in each of the two peripheral chambers. A single thickness of cellulose dialysis membrane (type 36, Union Carbide, Chicago, IL) was used to separate the cells. Immediately before dialysis, sodium fluoride (20 mg/20 ml) was added to the blood samples in order to prevent ongoing cellular metabolism; the pH of each drug-containing buffer solution and each sample of blood and plasma was measured and adjusted to the required pH value by the addition of either 0.1 M NaOH or 0.1 M HCl.

After dialysis for 6 hr, samples from each chamber were taken for drug concentration analysis and determination of pH. Preliminary experiments had verified equilibration by this time. To check for possible protein leakage across the dialysis membrane, resid-

Table 2 (continued)

Left atrial concentration		Brain concentration		Skeletal muscle concentration		Fat concentration	
Control	Acidosis	Control	Acidosis	Control	Acidosis	Control	Acidosis
15.2 <i>n</i> = 1	14.9 <i>n</i> = 1	9.8 ± 0.3 <i>n</i> = 3	18.1 ± 18.0 <i>n</i> = 2*	6.7 ± 7.5 <i>n</i> = 2	9.4 ± 9.0 <i>n</i> = 2	NA	NA
8.1 ± 11.2 <i>n</i> = 2*	9.0 ± 0.1 <i>n</i> = 3	14.4 ± 1.7 <i>n</i> = 4	17.3 ± 2.5 <i>n</i> = 5	6.6 ± 0.6 <i>n</i> = 3	7.1 ± 7.3 <i>n</i> = 2*	11.8 ± 1.5 <i>n</i> = 3	11.2 ± 9.3 <i>n</i> = 2*
9.4 ± 5.5 <i>n</i> = 2*	5.1 ± 0.1 <i>n</i> = 3	11.7 ± 0.1 <i>n</i> = 3	9.9 ± 1.6 <i>n</i> = 6	4.5 ± 0.1 <i>n</i> = 3	4.6 ± 5.5 <i>n</i> = 2*	3.6 ± 1.2 <i>n</i> = 3	2.2 ± 4.1 <i>n</i> = 2*
12.4 ± 13.8 <i>n</i> = 2*	9.6 ± 7.8 <i>n</i> = 2*	13.6 ± 0.7 <i>n</i> = 4	12.0 ± 2.2 <i>n</i> = 3	6.0 ± 1.0 <i>n</i> = 4	6.3 ± 7.0 <i>n</i> = 2*	4.2 ± 0.7 <i>n</i> = 4	7.0 ± 3.4 <i>n</i> = 2*
3.9 ± 3.8 <i>n</i> = 2*	3.4 ± 4.3 <i>n</i> = 2*	7.6 ± 0.7 <i>n</i> = 3	7.0 ± 0.1 <i>n</i> = 4	2.1 ± 0.4 <i>n</i> = 3	2.6 ± 0.3 <i>n</i> = 3	3.3 ± 0.6 <i>n</i> = 3	4.2 ± 0.6 <i>n</i> = 3
2.3 ± 2.2 <i>n</i> = 2*	1.8 ± 0.4 <i>n</i> = 3	4.1 ± 0.5 <i>n</i> = 4	3.5 ± 0.4 <i>n</i> = 5	0.9 ± 0.1 <i>n</i> = 4	1.7 ± 0.2 <i>n</i> = 3	2.4 ± 0.6 <i>n</i> = 3	2.1 ± 0.3 <i>n</i> = 3
1.2 ± 1.4 <i>n</i> = 2*	1.0 ± 0.8 <i>n</i> = 2*	2.4 ± 0.03 <i>n</i> = 3	1.4 ± 0.2 <i>n</i> = 4	1.0 ± 0.1 <i>n</i> = 4	0.6 ± 0.04 <i>n</i> = 3	1.2 ± 0.8 <i>n</i> = 4	1.3 ± 0.3 <i>n</i> = 3
5.8 ± 11.3 <i>n</i> = 2*	6.9 ± 1.6 <i>n</i> = 3	8.7 ± 0.3 <i>n</i> = 4	7.0 ± 0.3 <i>n</i> = 4	2.3 ± 0.5 <i>n</i> = 4	2.7 ± 0.1 <i>n</i> = 4	0.8 ± 0.1 <i>n</i> = 4	2.6 ± 0.7 <i>n</i> = 4

ual buffer was tested for the presence of protein with protein reagent strips (Albustix, Ames Company). Protein leakage did not occur on any occasion.

Determination of Lidocaine and Bupivacaine Concentrations in Blood, Plasma and Buffer. A rapid single extraction technique was developed for the assay of lidocaine and bupivacaine. Whole blood, plasma or buffer (0.5 ml) was added to an Eppendorf vial (1.5 ml) containing heparin (25 IU) and mepivacaine HCl (5 µg, 50 µL H₂O) as internal standard. NaOH (200 µL, 0.1 N) and toluene (200 µL) were added. The contents of the vial were vortex mixed for 1 min and then centrifuged at 6000 rpm for 3 min. One µL of the organic phase was removed with a microliter syringe and injected into a gas chromatograph equipped with nitrogen-phosphorous detection. A 2 m × 2 mm (inner diameter) column packed with 3% OV-17 on 100/120 mesh GAS-CHROM Q was used with nitrogen as the carrier gas at 30 ml/min. Column oven temperature was 245°C for bupivacaine and 230°C for lidocaine, whereas injector and detector temperatures were 250 and 300°C, respectively. Concentrations were determined from a standard curve prepared by the addition of known amounts of lidocaine and bupivacaine to appropriate samples obtained before exposure to these drugs.

Determination of Lidocaine and Bupivacaine Concentration in Tissues. Microtechniques were developed for the assay of lidocaine and bupivacaine in the various

tissues. After the addition of mepivacaine (0.5 µg in 50 µL H₂O) as internal standard and HCl (200 µL, 2N), weighed biopsies (50–100 mg) were homogenized in 1.5-ml Eppendorf vials using an electric drill to turn a Teflon pestle. After homogenization, NaOH (200 µL, 5N) and 500 µL of solvent (98% heptane; 2% isoamyl alcohol) were added and the contents mixed for 1 min and then centrifuged for 3 min. The organic layer was transferred to fresh Eppendorf vials containing HCl (200 µL, 2N) and mixed and centrifuged as before. The organic layer was discarded, and NaOH (200 µL, 5N) and 200 µL of the same solvent were added to the aqueous phase and mixed and centrifuged as before. After this extraction, 1–3 µL of the organic phase was injected into a gas chromatograph using the conditions described above. A standard curve was prepared by the addition of known amounts of lidocaine and bupivacaine to heart tissue not previously exposed to these drugs. For analysis of brain drug concentrations, a similar extraction procedure was followed with an additional solvent washing of the acid phase using diethyl ether (500 µL) prior to the final extraction in order to minimize lipid contamination.

Statistical Methods

The acid-base status of the drug treatment groups, both before and during acidosis, was compared by Student's unpaired *t*-tests on measured pH and lactate concentrations. In addition, the effects of acidosis

on tissue:blood partition coefficients were compared by three factor analysis (drug $\times$ acidosis $\times$ tissue) of variance with repeated measures on two factors (acidosis, tissue) (17). Partition coefficients were converted to natural logarithms prior to analysis to provide a more symmetrical distribution. A P value less than 0.05 was considered to be of statistical significance.

Results

Acid-Base Parameters

During the control period, there were no significant differences in blood pH between lidocaine- or bupivacaine-treated animals when comparing arterial, coronary sinus, or sagittal sinus blood samples ($P > 0.4$) (Table 1). With the induction of acidosis, there was no significant difference between lidocaine or bupivacaine-treated animals in the degree of decrease in pH when comparing either arterial, coronary sinus or sagittal sinus blood samples ($P > 0.5$) (Table 1). Arterial lactate concentrations increased markedly in all animals with the induction of acidosis (Table 1).

Blood and Tissue Drug Concentrations and Partition Coefficients

Blood and tissue concentration data are presented in Table 2. The effect of acidosis on partition coefficients of the two drugs differed, but the pattern was different in different tissues ($P < 0.05$). This significant three-factor interaction was examined by studying the simple interaction effects (drug $\times$ acidotic state) in each tissue using error terms based only on data obtained in that tissue. In both the left ventricle and left atrium, acidosis decreased partition coefficients for both drugs ($P < 0.005$ in each case). In the brain, the effects of acidosis on partition coefficients of lidocaine and bupivacaine were significantly different ($P < 0.025$). In skeletal muscle, acidosis did not affect the partition coefficient of either drug ($P > 0.5$) (Fig. 1).

Local Anesthetic Pharmacokinetics during Induced Acidosis

There were no systematic effects of acidosis on mean hepatic blood flow, mean hepatic local anesthetic clearance, or flux (Table 3).

Binding of Local Anesthetics in Blood and Plasma

Figure 2 shows the unbound concentrations plotted against the total plasma concentrations of each drug

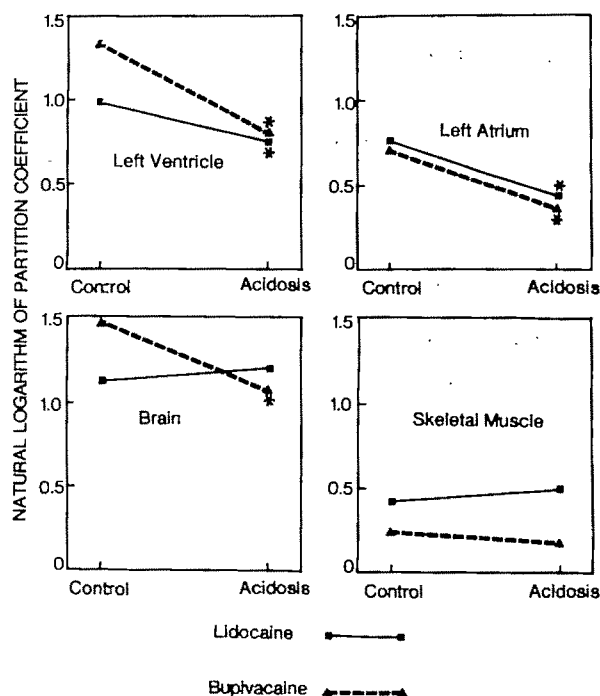


Figure 1. The effect of combined respiratory-metabolic acidosis on the in vivo tissue:blood partition coefficients of lidocaine and bupivacaine. Partition coefficients were converted to their natural logarithms to produce a more symmetrical distribution before statistical analysis. Partition coefficients for left ventricle and left atrium decreased ($P < 0.005$ for both agents). For the brain, there was a significant difference in the effects of acidosis on the partition coefficients of lidocaine and bupivacaine ($P < 0.025$); partition coefficients for skeletal muscle were not affected by acidosis for either drug ($P > 0.05$). Asterisks indicate statistical significance as described above.

at pH 7.4 and 7.0. There were quantitative differences between animals, but the rank order of binding was the same for both drugs. These differences were not obviously related to differences in the animals' hematologic or biochemical profiles, both of which were within the normal range for sheep (9). For both drugs, the unbound and total drug concentrations were linearly related over a large concentration range. The percentage unbound of both drugs was less at the lower pH, however, the difference was more obvious for bupivacaine for which binding was substantially greater than lidocaine (Fig. 3). Deviations from a constant percentage bound occurred only at sub-microgram concentrations of each drug.

At both pH values, the drug percentage bound in whole blood was substantially the same as that in plasma for bupivacaine, but for lidocaine it was usually less. In the blood of sheep 3 at both values of pH, and in the blood of sheep 1 at pH 7.0, the calculated percentage unbound at several concentrations exceeded 100. Thus it is possible that equilibrium had not been established, although the preliminary ex-

periments had suggested that the gains of prolonging dialysis would be small. The ratio of the total concentrations in the blood and plasma dialysis cells did not systematically differ as a function of pH (Table 4). In each case, the measured pH at the conclusion of dialysis was within 0.1 pH units of the predialysis value.

Discussion

For this study, it was considered necessary to determine tissue distribution of lidocaine and bupivacaine at "steady state" arterial blood and tissue concentrations and normal acid-base status before repeating the measurements during acidosis induced by a method that closely simulates the events during local anesthetic toxicity. This design was developed in order to overcome possible objections to previous studies in which tissue samples were obtained postmortem or with rapidly changing arterial concentrations under "non-steady state" conditions (6,18).

The other major consideration in the design of this study was the use of each animal as its own control. It was anticipated that there could be appreciable variability between animals with respect to drug concentrations in tissues and blood and in the ratio of these concentrations but that there would be a high degree of consistency within animals; this was subsequently borne out (Table 2). As examples, the mean (and SD) of the mean lidocaine left ventricular concentrations under control and acidotic conditions in the four animals were, respectively, 2.7 (0.6) and 2.2 (0.4) mg/g, i.e., with respective coefficients of variation of 22 and 18%. In contrast, there was remarkable consistency within animals such that the mean (and SD) of the ratio of the mean lidocaine left ventricular concentrations during acidotic and control conditions in the four animals was 0.81 (0.07), i.e., a coefficient of variation of 9%. The equivalent respective coefficients of variation for the same parameters for bupivacaine were 74, 50, and 18%. This degree of consistency within animals permitted statistically significant conclusions to be drawn from a small sample size by the use of longitudinal experimental design.

The present study simulated the clinical condition of combined metabolic and respiratory acidosis reported to occur during local anesthetic toxicity (19) by the combination of increased skeletal muscle lactate production and hypoventilation. In this way, it simulates the conditions experienced by the heart rather than the brain, i.e., the conditions induced resulted in perfusion of the heart and brain with acidotic arterial blood containing high concentrations of lactic acid and carbon dioxide. The influence of coexisting

Table 3. Mean Total Body Drug Clearance, Hepatic Blood Flows, Hepatic Drug Extraction Ratios, and Hepatic Local Anesthetic Clearances and Fluxes of Animals Receiving Infusions

Sheep	Mean total body clearance (L/Min)		Hepatic blood flow (L/min)		Hepatic local anesthetic extraction ratio		Hepatic local anesthetic clearance (L/min)		Hepatic local anesthetic flux (mg/min)	
	Control	Acidosis	Control	Acidosis	Control	Acidosis	Control	Acidosis	Control	Acidosis
Lidocaine-treated group										
A	0.73	1.04	—	—	—	—	—	—	—	—
B	1.09	1.00	1.23 ± 0.18 n = 4	0.96 ± 0.12 n = 4	0.93 ± 0.01 n = 4	0.83 ± 0.11 n = 4	1.14 ± 0.17 n = 4	0.80 ± 0.19 n = 4	5.81	4.39
C	2.04	2.27	2.08 ± 0.23 n = 4	2.40 ± 0.42 n = 3	0.88 ± 0.05 n = 4	0.81 ± 0.10 n = 3	1.83 ± 0.14 n = 4	2.03 ± 0.54 n = 3	5.31	5.17
D	1.40	1.51	1.36 ± 0.07 n = 3	1.89 ± 0.71 n = 4	0.95 ± 0.01 n = 3	0.87 ± 0.06 n = 4	1.29 ± 0.07 n = 3	1.61 ± 0.52 n = 4	5.63	6.32
Bupivacaine-treated group										
E	1.06	0.79	—	—	—	—	—	—	—	—
F	1.16	1.13	1.59 ± 0.09 n = 4	1.49 ± 0.17 n = 5	0.86 ± 0.02 n = 4	0.83 ± 0.03 n = 5	1.36 ± 0.09 n = 4	1.24 ± 0.12 n = 5	1.83	1.70
G	1.77	1.70	1.83 ± 0.08 n = 4	2.21 ± 0.21 n = 4	0.81 ± 0.02 n = 4	0.75 ± 0.07 n = 4	1.48 ± 0.12 n = 4	1.65 ± 0.37 n = 4	1.00	1.17
H	1.22	1.28	—	—	—	—	—	—	—	—

Infusions, to produce steady state arterial concentrations, were of bromosulfthalein (BSP) and either lidocaine or bupivacaine during both control and acidotic periods. Paired blood samples (n = 3-5) were taken from arterial and hepatic vein catheters during the last 15 min of the control and acidotic periods.

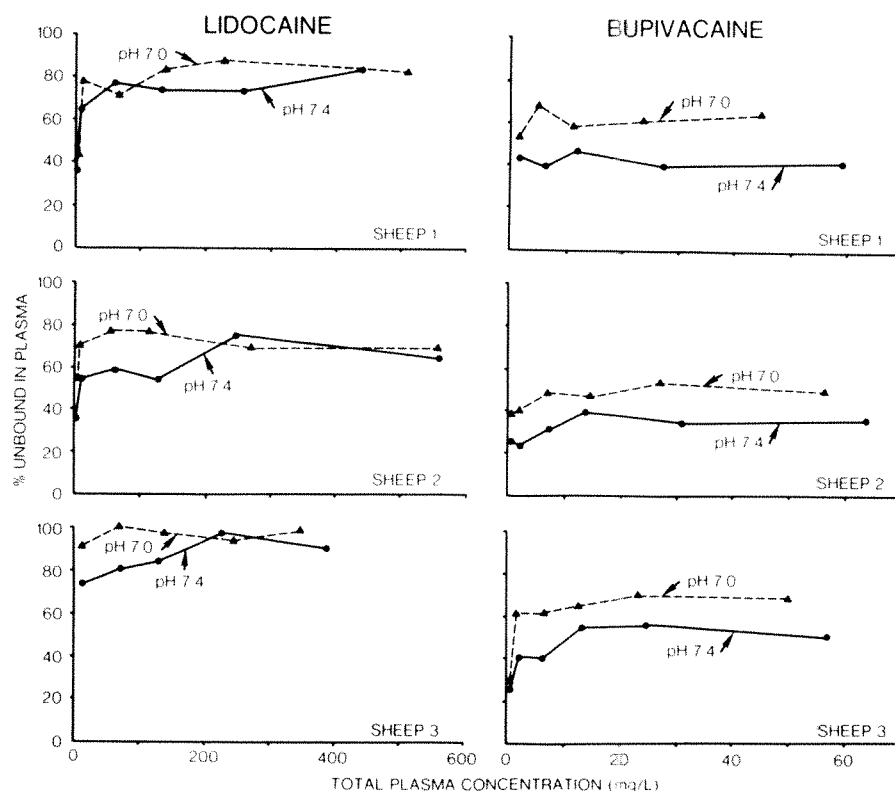


Figure 2. Comparison of the percentage plasma binding of lidocaine and bupivacaine at pH 7.0 and 7.4 in three sheep not previously exposed to any drugs. The total concentrations examined span the ranges encountered in local anesthetic-induced toxicity.

hypoxia on tissue concentrations of these drugs was not examined in this experimental protocol, nor was the influence of acidosis on intracellular concentrations of free drug. These questions need to be addressed in future studies.

For both drugs, acidosis produced significant reductions in tissue:blood partition coefficients in both the left ventricle and the left atrium. Therefore, these data not only fail to support the original hypothesis, but an effect with respect to the imposition of acidosis was opposite to that which was predicted. In fact, these unexpected results may be explained by study of the problem from first principles. The metabolic component of the acidosis was not generated in these tissues. Therefore, it would be predicted that the extent to which intracellular pH in these organs is less than extracellular pH would be reduced, if heart and brain oxygen demands are met during acidosis. Thus, increased partitioning of basic drugs into these organs would not be expected with systemic acidosis generated in skeletal muscles.

It is interesting to note that skeletal muscle partition coefficients did not change with acidosis. During the induced skeletal muscular hyperactivity with its resultant increased lactic acid production, skeletal muscle perfusion increases, and this increases the rate of removal of lactic acid from that tissue (14). Therefore, the local gradients from (lowered) intracellular

pH to (lowered) extracellular pH might not change peripherally.

Other investigators have measured brain local anesthetic concentrations and intracellular pH during convulsions. This has provided insights into the importance of the metabolic status of that organ in determining transmembrane drug fluxes. In rats, convulsions increased the cerebral concentrations of lidocaine in accordance with decreased brain intracellular pH (20,21). The decrease in brain pH presumably was caused by an increase in cerebral metabolic rate in response to the convulsions. However, when coexisting extracellular acidosis was corrected by artificial ventilation of the animals (resulting in little acute change in intracellular pH), there resulted a further increase in brain lidocaine concentration. In the present studies, local anesthetic concentrations were not great enough to induce convulsions in the anesthetized animals. Therefore, it is unlikely that a decrease in brain intracellular pH occurred as in the studies of Simon et al. (20,21). As for the heart, brain:blood partition coefficients would be expected to decrease under the conditions of this study. The greater effect of acidosis on the brain:blood partition coefficient for bupivacaine compared to lidocaine supports the predictions of the pH partition hypothesis for this tissue.

Although increased unbound fractions of lidocaine

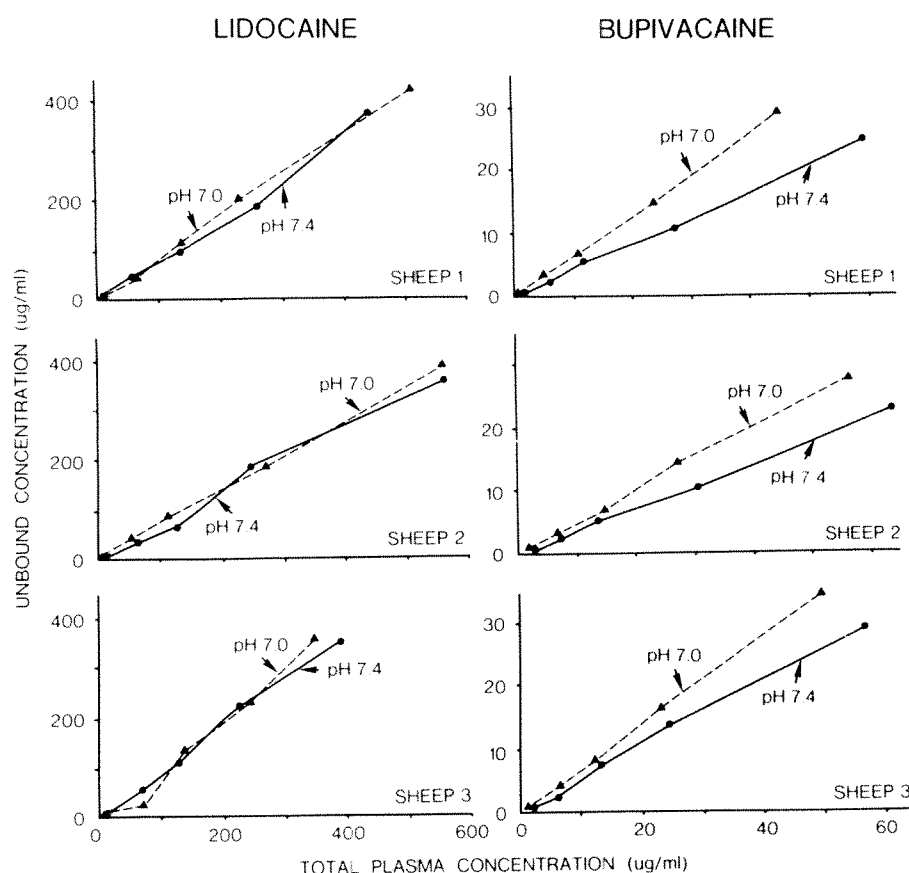


Figure 3. The relation between unbound and total plasma concentrations of lidocaine and bupivacaine at pH 7.0 and pH 7.4 in three sheep not previously exposed to any drugs. The total concentrations examined span the ranges encountered in local anesthetic-induced toxicity.

and bupivacaine in plasma result from acidosis under in vitro conditions, this would seem, from the results of this study, to have little influence on tissue distribution of these drugs in vivo. Although the unbound plasma concentrations of both agents may increase during acidosis, it is possible that the potential for increased tissue uptake is offset by an increased fraction of the unbound drug existing in the conjugate acid form that may be unavailable for tissue distribution.

In recent experiments, the plasma binding of these local anesthetics has been rationalized as being accounted for by two classes of binding sites for which there are different affinity constants (22-24). It is now generally accepted that the two classes of binding sites for basic drugs such as lidocaine and bupivacaine in human plasma correspond to a high affinity-low capacity site on α -1-acid glycoprotein (25) and a low affinity-high capacity binding site, possibly on albumin (26). The former is the predominant binding protein in the low concentration range, and the latter is predominant in the higher concentration range after saturation has occurred of α -1-acid glycoprotein sites (27).

In the present studies, frequently observed nonlin-

Table 4. Values of the Blood:Plasma Total Drug Concentration Ratios at the End of 6 Hours Equilibrium Dialysis

	Sheep 1	Sheep 2	Sheep 3
Lidocaine	1.09	0.80	0.89
pH 7.4	(0.11)	(0.09)	(0.08)
Lidocaine	0.79	0.89	0.90
pH 7.0	(0.10)	(0.20)	(0.13)
Bupivacaine	0.82	0.91	0.95
pH 7.4	(0.12)	(0.10)	(0.09)
Bupivacaine	0.77	0.98	1.05
pH 7.0	(0.12)	(0.13)	(0.12)

The means and standard deviations of the five highest concentrations are shown.

ear patterns of binding with increasing drug concentration were not readily apparent, i.e., either the high affinity-low capacity was saturated at the extreme low end of the concentration range examined or the concentration range was not extended far enough. The curvature in the submicrogram region plotted in Figure 2 suggests that the former is more likely. Although it has been determined that there are at least two classes of binding sites for lidocaine and bupivacaine in sheep plasma, as in human plasma (22), it is not

known whether sheep have an α -1-acid glycoprotein fraction that may be equated to the high-affinity site of human plasma, and there is no radial immunodiffusion assay currently available which is suitable to determine the concentration of such a protein specifically for the sheep. Extension of the drug concentration range to provoke saturation was of little consequence because the range examined included studies of the drug concentration range known to be lethal. Whether the low affinity "binding" is macromolecular association of drug or simple partition into lipoprotein (27) is open to question. The marked linearity of the "unbound" fraction suggests that the latter is possible, although a greater effect of pH for lidocaine might have been expected on the basis of change in its fraction ionized at the lower value of pH. The possibility of nonspecific "binding" or partition is strengthened by the observation of Denson et al. (24) that bupivacaine binding is unaffected by the presence of diazepam. For the low affinity-high capacity binding to be a specific interaction with albumin, it would have been expected that bupivacaine binding would have been inhibited, to some extent, in the presence of diazepam, which is known to have high affinity for albumin (24).

Differences in the absolute levels of plasma protein binding for these drugs thus have not produced identifiable differences in myocardial or cerebral uptake. This may be explained by the fact that for both drugs, binding to, or other association with, protein at lethal concentrations was of such a low affinity that organ distribution of either drug was not affected. Moreover, traditional teaching that only the unbound portion of drug is available for transport from blood into tissues (such as brain and heart) may now be questioned in the light of data showing that drugs such as lidocaine which are bound to plasma globulins may enter tissue cells in vivo (28).

In summary, combined respiratory-metabolic acidosis produced no systematic changes in the total or hepatic clearance of lidocaine or bupivacaine. There were alterations in myocardial:blood partition coefficients for both lidocaine and bupivacaine, but the direction of these changes showed partitioning from the heart into the blood. Predictions based on the pH partition hypothesis about the effects of acidosis on myocardial:blood partition coefficients for bupivacaine relative to lidocaine have not been supported; in fact, the movement was in the opposite direction.

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Hepatic Circulation during Surgical Stress and Anesthesia with Halothane, Isoflurane, or Fentanyl

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GELMAN S, DILLARD E, BRADLEY EL. Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane, or fentanyl. *Anesth Analg* 1987;66:936-43.

Hepatic blood flow and the oxygen supply/uptake relation were studied in 19 miniature pigs using labeled microspheres. Changes in hepatic arterial blood flow and portal blood flow, as well as total hepatic blood flow during halothane anesthesia were more closely associated with changes in mean arterial pressure (MAP) and cardiac output than during anesthesia with isoflurane or fentanyl. Halothane or isoflurane administered in concentrations that decreased MAP by approximately 30% were accompanied by decreases in hepatic oxygen delivery ($\text{DO}_{2\text{th}}$) averaging 46% during halothane and 31% during isoflurane anesthesia and parallel decreases in hepatic blood flow. In concentrations that decreased MAP by 50%, halothane and isoflurane decreased $\text{DO}_{2\text{th}}$ 61 and 37%, respectively. $\text{DO}_{2\text{th}}$ was maintained (statistically insignificant, 23% increase) during both doses of fentanyl administered (20 $\mu\text{g/kg}$ followed by 0.17 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and 50 $\mu\text{g/kg}$ followed by 0.42 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Hepatic oxygen uptake increased 50% during fentanyl and

was maintained at baseline levels during both doses of halothane and isoflurane anesthesia. Oxygen content in hepatic venous blood was maintained at baseline levels during fentanyl and isoflurane administration and was decreased by both concentrations of halothane anesthesia. The hepatic oxygen supply demand ratio was maintained at baseline levels after both doses of fentanyl and during isoflurane administered in a concentration that decreased blood pressure 30%; the ratio decreased during isoflurane administered in a concentration decreasing blood pressure by 50% and during both doses of halothane anesthesia. The data suggest that during surgical stress, anesthesia, using fentanyl or isoflurane in a concentration decreasing blood pressure by $\leq 30\%$, provides adequate hepatic oxygen supply, whereas anesthesia with isoflurane in a concentration decreasing blood pressure $>30\%$, or with halothane in any concentration studied, results in inadequate hepatic oxygen supply.

Key Words: LIVER—blood flow, oxygenation. ANESTHETICS, VOLATILE—isoﬂurane, halothane. ANESTHETICS, INTRAVENOUS—fentanyl.

Inhalational anesthetics decrease total hepatic blood flow (THBF) in a dose-related fashion (1). Different anesthetics can decrease THBF to different degrees and can also affect the hepatic circulation in different ways. For example, halothane decreases THBF more than isoflurane (2-4). Moreover, isoflurane decreases THBF primarily by a reduction in portal blood flow (PBF), while hepatic arterial blood flow (HABF) is increased, apparently maintaining hepatic oxygen supply. On the other hand, halothane decreases both HABF and PBF with a more prominent reduction in hepatic oxygen supply than isoflurane when used in equipotent concentrations (2-4).

The effects of the widely used synthetic opioid fentanyl on the hepatic circulation have not been adequately studied. However, in experiments with isolated intestinal loop preparations in which perfusion pressure was artificially maintained, fentanyl led to a dose-related intestinal vasodilation and a decrease in oxygen uptake, most likely due to a decrease in oxygen requirement (5). The decrease in PBF reported during anesthesia with halothane is closely related to the decrease in mean arterial pressure (MAP) and cardiac output (CO) (2,6). Fentanyl administration, even in large doses, is accompanied by remarkably stable hemodynamics, including MAP and CO (7). Therefore, it seems conceivable that during anesthesia using fentanyl, PBF might not decrease as it usually does during halothane or isoflurane anesthesia and, also, oxygen content in portal blood might increase as a result of a decrease in oxygen requirement in the intestines. In this case, the hepatic blood and oxygen supply during anesthesia with fentanyl would be

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maintained at better levels than during inhalation anesthesia.

Though this hypothesis sounds reasonable, the situation can be complicated by another rather important factor, namely, surgical stress. Indeed, surgical stress may affect the hepatic circulation more dramatically than anesthesia itself (8,9). Moreover, anesthesia may play a modifying role in the complex of surgery and anesthesia: similar surgical procedures may be accompanied by different degrees of hepatic circulatory disturbances with different types of anesthesia (8). Therefore, the modifying role of anesthesia in the development of hepatic circulatory disorders during surgery can be more relevant clinically than the effect of one or another anesthetic itself on the hepatic circulation. Thus, the main hypothesis of the present study can be said to be that similar levels of surgical stress during different types of anesthesia are accompanied by different hepatic circulatory disturbances and different changes in the hepatic oxygen supply/uptake relation. The study is designed to test this and another hypothesis, namely that during surgical stress, anesthesia, using fentanyl, is associated with stable systemic and regional (splanchnic) hemodynamics and well-maintained hepatic blood flow and oxygen supply.

Materials and Methods

The study was performed on 19 miniature pigs weighing 20–25 kg. The animals were anesthetized with methohexital, 20–25 mg/kg intramuscularly (IM). Muscle relaxation was achieved with pancuronium, 0.1 ml/kg intravenously (IV). Surgical preparation was performed under anesthesia with nitrous oxide (70 vol%) in oxygen and additional methohexital IV, 1–2 mg/kg two–three times per hour, or whenever reflex limb or any movement returned. Controlled ventilation was provided with an Air-Shield respirator through an endotracheal tube to maintain PaCO_2 between 35–40 mm Hg. Rectal temperature was monitored and kept at 38° C by an electrical heating pad throughout the experiments. Femoral arteries and veins were exposed in both groins; an intravenous catheter inserted into the inferior caval vein through one of the femoral veins was used to infuse lactated Ringer's solution at a rate of 5 ml·kg⁻¹·hr⁻¹. The aorta was cannulated through both femoral arteries: one catheter was used to monitor arterial blood pressure, the other to withdraw reference samples during microsphere injections. After the vessels in the groins were cannulated, 80 ml of blood was taken from the pig for future blood replacement during microsphere injections and collection of reference samples. Blood volume was re-

placed with 300 ml lactated Ringer's solution. A flow-directed catheter was introduced into the pulmonary artery via the right jugular internal vein for cardiac output determinations by thermodilution. Surgical preparation required a left thoracotomy, placement of a left atrial catheter for microsphere injections, and monitoring of left atrial pressure (LAP). A laparotomy was performed and a catheter introduced into the portal vein through the venous wall; another catheter was inserted into the left hepatic vein through the inferior caval vein subdiaphragmatically above the liver in such a way as to assure that the tip lay in a free position in the hepatic vein. When surgical preparation was completed, nitrous oxide was discontinued and the lungs ventilated with oxygen and nitrogen ($\text{FiO}_2 = 0.5$). After 30 min of stabilization, the first set of measurements was obtained (Stage I—baseline values). Systolic, diastolic, and mean arterial pressures (SAP, DAP, MAP, respectively), pulmonary artery pressures (PAP), LAP, and heart rate (HR) were recorded. Arterial, portal venous and hepatic venous blood samples were obtained, and blood gas tensions and pH were measured using an Instrumentation Laboratory (IL) 813 pH/blood gas analyzer; oxygen content in these three samples was determined with an IL 282 co-oximeter. Cardiac output was determined in triplicate using thermodilution. A set of microspheres labeled with one of three isotopes was injected into the left atrium for hepatic blood flow determinations. During injection of microspheres, reference samples were collected from the aorta for 3 min at a rate of 10 ml/min; 40 ml of blood was replaced.

The pigs were then randomly divided into three groups: fentanyl (five pigs); halothane (six); and isoflurane (eight). Pigs in the halothane and isoflurane groups received the inhalational anesthetics in concentrations adequate to decrease and maintain MAP at approximately 70% of baseline values. Pigs given fentanyl received 20 µg/kg fentanyl IV, followed by an infusion of 0.17 µg·kg⁻¹·min⁻¹, a protocol designed to provide a relatively stable concentration of the drug in the blood (10). After 30 min of stable MAP and end-expired halothane or isoflurane concentrations (monitored with an Engström gas analyzer—EMMA) a second set of measurements was obtained (Stage II). These determinations included SAP; DAP; MAP; PAP; LAP; arterial, portal venous, and hepatic venous blood gas tensions; and pH, as well as oxygen content. A second set of microspheres was injected while reference samples were collected from the aorta at the same rate of 10 ml/min. The remaining 40 ml of blood that had been collected at the beginning of the experiments was infused.

In the fentanyl group, an additional dose of 50

$\mu\text{g/kg}$ was administered intravenously followed by infusion of $0.42 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. In the halothane and isoflurane groups, the concentrations of halothane and isoflurane were increased to decrease blood pressure to approximately 50% of baseline values. After 30 min of stable hemodynamics and end-expired concentrations of halothane and isoflurane, a third set of measurements was obtained (Stage III) as described earlier.

At each stage, $1.2\text{--}1.8 \times 10^6$ microspheres of 15 ± 1.5 (SD) μm in diameter were injected into the left atrium to measure CO and liver blood flow. Reference blood samples were collected from the distal aorta at a constant rate of 10 ml/min for 3 min, 10 sec before injection of microspheres. The microspheres were labeled with ^{85}Cr , ^{95}Nb , and ^{113}Sn and suspended in a 10% dextran solution with Tween 80. Each shipment of microspheres (3M, St. Paul, Minnesota) was checked for sphere size, presence of fragmentation, and status of aggregation. The microspheres were mixed in a special injector with 3–5 ml normal saline solution (11) and injected into the left atrium immediately after the mixture was shaken vigorously for 2 min on a Vortex mixer. The injection of spheres was made over a period of 30 sec, followed by an additional 20 ml normal saline solution at body temperature. After the third set of microspheres was injected, the heart was arrested with IV potassium chloride. The kidneys and splanchnic organs were removed for dissection, activity counting, and blood flow calculations. Activity found in the liver was used for HABF calculations, whereas activity in all other splanchnic organs was used to calculate PBF.

The radioactivity in the tissue and blood samples was analyzed with a Tracor 2250 gamma counting system (Tracor Northern, Middleton, WI) (12,13), which utilizes the least-squares fitting technique to resolve the amount of radioactivity contributed by each isotope in γ -ray spectra obtained by NaI detector for individual tissue and blood samples (13). The experiment was disregarded if the difference in blood flow through the cortex of the left and right kidney was $>15\%$, because greater values were considered indicative of inadequate mixing of microspheres in the bloodstream.

The data were summarized as the mean $\pm$ SEM for each of the three groups and the three stages combined. The original variables were also expressed as the percent change from Stage I values in the last two stages. Comparison between groups at each stage utilized a one-way analysis of variance. Comparison of data within groups used the repeated measures analysis of variance. Tests of significance for percent changes from baseline values used a one-sample *t*-test. Multiple comparisons of group and stage means

Table 1. Baseline Values (Stage I) of Main Systemic and Hepatic Hemodynamic Variables and Hepatic Oxygen Supply (Mean $\pm$ SEM)

Variable	Fentanyl	Halothane	Isoflurane
MAP	109 $\pm$ 2.4	115 $\pm$ 3.9	113 $\pm$ 3.8
CO	2 $\pm$ 0.1	2 $\pm$ 0.2	2 $\pm$ 0.3
PP	11 $\pm$ 0.5	13 $\pm$ 0.6	11 $\pm$ 0.5
HVP	8 $\pm$ 0.5	12 $\pm$ 0.8	9 $\pm$ 1.0
PBF	0.282 $\pm$ 0.019	0.222 $\pm$ 0.022	0.239 $\pm$ 0.027
HABF	0.203 $\pm$ 0.043	0.196 $\pm$ 0.035	0.206 $\pm$ 0.025
THBF	0.485 $\pm$ 0.054	0.418 $\pm$ 0.054	0.444 $\pm$ 0.041
SPVR	215.98 $\pm$ 21.39	265.67 $\pm$ 31.33	251.56 $\pm$ 29.61
HAVR	571.13 $\pm$ 95.26	643.52 $\pm$ 145.30	568.96 $\pm$ 81.10
PPVR	351.96 $\pm$ 20.95	475.11 $\pm$ 39.17	469.51 $\pm$ 60.04
PVR	9.48 $\pm$ 1.31	7.43 $\pm$ 2.58	6.94 $\pm$ 2.57
CvO ₂ pv	11.2 $\pm$ 1.07	12.5 $\pm$ 1.61	10.6 $\pm$ 0.38
CvO ₂ hv	7.6 $\pm$ 1.16	8.9 $\pm$ 0.90	8.2 $\pm$ 1.03
Do ₂ th	0.067 $\pm$ 0.010	0.061 $\pm$ 0.008	0.062 $\pm$ 0.005
Vo ₂ th	0.027 $\pm$ 0.004	0.022 $\pm$ 0.004	0.025 $\pm$ 0.004
Do ₂ + Vo ₂	2.57 $\pm$ 0.546	3.15 $\pm$ 0.607	2.92 $\pm$ 0.454
Do ₂ - Vo ₂	0.04 $\pm$ 0.011	0.04 $\pm$ 0.008	0.04 $\pm$ 0.006

Abbreviation: MAP, mean arterial pressure in mm Hg; CO, cardiac output in L/min; PP, HVP, portal venous pressure and hepatic venous pressure in mm Hg, respectively; PBF, HABF, THBF, portal blood flow, hepatic arterial blood flow, total hepatic blood flow in $\text{ml}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$, respectively; SPVR, HAVR, PPVR, PVR, splanchnic vascular resistance, hepatic arterial vascular resistance, preportal vascular resistance, portal venous resistance in $\text{mm Hg}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$, respectively; CvO₂pv, CvO₂hv, oxygen content in portal venous and hepatic venous blood in ml O₂/dl, respectively; Do₂th, Vo₂th, hepatic oxygen delivery, hepatic oxygen uptake in $\text{ml O}_2\cdot\text{min}^{-1}\cdot\text{g}^{-1}$, respectively; Do₂ + Vo₂, Do₂ - Vo₂, hepatic oxygen supply/uptake ratio, hepatic oxygen supply/uptake gradient in $\text{ml O}_2\cdot\text{min}^{-1}\cdot\text{g}^{-1}$. There is no significant difference between groups in any variable.

used Fisher's protected least significant difference test. Pearson correlation coefficients were used to measure the association between pairs of measurements (14). Differences were considered statistically significant if $P < 0.05$.

Results

Baseline hemodynamic variables and baseline hepatic oxygen supply/uptake values are presented in Table 1. There were no significant differences in any variables among the three groups. End-expired concentrations of halothane and isoflurane needed to decrease MAP by 30% were 0.95 ± 0.11 and $1.22 \pm 0.17\%$, respectively. End-expired concentrations of halothane and isoflurane needed to decrease blood pressure 50% were 1.5 ± 0.21 and $2.0 \pm 1.21\%$, respectively. During Stages II and III of observation, MAP increased slightly in the fentanyl group and decreased according to experimental design in the halothane and isoflurane groups. Left atrial pressure did not change significantly throughout the experiments. Cardiac output did not change significantly in the

Table 2. Main Systemic and Hepatic Hemodynamic Variables and Hepatic Oxygen Supply During Stage II (Mean $\pm$ SEM)

Variable	Fentanyl	Halothane	Isoflurane
MAP	118 $\pm$ 4.4 ^a	70 $\pm$ 3.8 ^{a,b}	71 $\pm$ 2.7 ^{a,b}
CO	92 $\pm$ 9.0	72 $\pm$ 3.8 ^{a,b}	87 $\pm$ 8.0
PP	97 $\pm$ 4.4	94 $\pm$ 4.4	82 $\pm$ 4.5 ^a
HVP	105 $\pm$ 3.1	95 $\pm$ 4.0	84 $\pm$ 5.4 ^a
PBF	122.4 $\pm$ 9.2	68.4 $\pm$ 4.8 ^{a,b}	91.3 $\pm$ 8.5
HABF	114.4 $\pm$ 35.5	59.0 $\pm$ 6.9 ^{a,b}	57.8 $\pm$ 9.7 ^{a,b}
THBF	117.7 $\pm$ 13.4	63.2 $\pm$ 3.5 ^{a,b}	75.2 $\pm$ 7.7 ^a
SPVR	104.9 $\pm$ 8.7	107.8 $\pm$ 7.2	97.9 $\pm$ 8.6
HAVR	132.2 $\pm$ 23.8	123.9 $\pm$ 18.6	140.5 $\pm$ 19.0
PPVR	99.5 $\pm$ 4.3	100.6 $\pm$ 9.0	81.2 $\pm$ 8.2
PVR	56.4 $\pm$ 16.9	131.8 $\pm$ 35.5	119.5 $\pm$ 37.8
CvO ₂ pv	111.5 $\pm$ 10.1	77.7 $\pm$ 7.2 ^{a,b}	99.9 $\pm$ 7.3 ^c
CvO ₂ hv	91.3 $\pm$ 10.8	54.8 $\pm$ 5.6 ^{a,b}	94.9 $\pm$ 23.4
DO ₂ th	124.1 $\pm$ 16.2	54.1 $\pm$ 5.1 ^{a,b}	68.8 $\pm$ 9.6 ^{a,b}
$\dot{V}O_{2$ th	149.2 $\pm$ 27.7 ^a	97.3 $\pm$ 21.8	80.0 $\pm$ 12.6 ^b
DO ₂ $\div$ $\dot{V}O_2$	89.9 $\pm$ 14.2	63.3 $\pm$ 7.9 ^a	103.3 $\pm$ 23.9
DO ₂ - $\dot{V}O_2$	109.7 $\pm$ 21.0	34.7 $\pm$ 3.9 ^{a,b}	74.2 $\pm$ 20.8 ^c

See footnote to Table 1 for abbreviations. All values are expressed in percent of baseline (Stage I) values.

^a*P* < 0.05 vs baseline values.

^b*P* < 0.05 vs fentanyl.

^c*P* < 0.05 vs halothane.

fentanyl group during Stage II or Stage III, and was also maintained during Stage II of isoflurane anesthesia. In the halothane group, however, CO was significantly below baseline levels at both Stages II and III; CO was also below baseline during Stage III with isoflurane (Tables 2 and 3, Fig. 1). Portal blood flow, HABF, and therefore THBF were maintained at baseline levels in the fentanyl group, but decreased in both groups of pigs given inhalation anesthesia in a dose-related fashion (Tables 2 and 3). Calculated vascular resistance in the splanchnic system did not change during the second stage of experiments but some decreases in vascular resistance were observed in the third stage of observation (Tables 2 and 3). Hepatic oxygen supply was well maintained with fentanyl but decreased in a dose-related fashion during anesthesia with inhalational anesthetics. The decrease in hepatic oxygen supply was more severe in pigs given halothane. Hepatic oxygen uptake was maintained during both stages of observation with halothane and isoflurane, and increased in pigs given fentanyl (Fig. 2).

The observed changes in hepatic oxygen supply and hepatic oxygen uptake resulted in maintenance of hepatic oxygen supply/uptake ratio in pigs given fentanyl or isoflurane during the second stage of experiments, and decreased in pigs given halothane during both stages of experiments, as well as in pigs

Table 3. Main Systemic and Hepatic Hemodynamic Variables and Hepatic Oxygen Supply During Stage III (Mean $\pm$ SEM)

Variable	Fentanyl	Halothane	Isoflurane
MAP	117 $\pm$ 6.5 ^a	46 $\pm$ 2.3 ^{a,b,d}	49 $\pm$ 2.6 ^{a,b,d}
CO	82 $\pm$ 7.0	48 $\pm$ 4.8 ^{a,b,d}	68 $\pm$ 5.0 ^{a,c}
PP	88 $\pm$ 6.4	100 $\pm$ 2.1	87 $\pm$ 4.8 ^a
HVP	90 $\pm$ 9.0	98 $\pm$ 3.1	92 $\pm$ 7.5
PBF	124.2 $\pm$ 12.0	55.7 $\pm$ 3.7 ^{a,b,d}	96.5 $\pm$ 11.1 ^c
HABF	83.7 $\pm$ 17.4	47.1 $\pm$ 11.5 ^{a,b}	39.7 $\pm$ 5.6 ^{a,b}
THBF	107.9 $\pm$ 12.4	49.9 $\pm$ 5.8 ^{a,b,d}	69.1 $\pm$ 8.3 ^{a,b}
SPVR	114.2 $\pm$ 7.4	84.2 $\pm$ 7.9	70.2 $\pm$ 8.5 ^{a,b,d}
HAVR	159.2 $\pm$ 19.9 ^c	118.2 $\pm$ 31.0	127.5 $\pm$ 16.7
PPVR	98.8 $\pm$ 4.4	70.5 $\pm$ 4.7 ^{a,b}	51.3 $\pm$ 7.3 ^{a,b,d}
PVR	63.6 $\pm$ 30.9	155.3 $\pm$ 38.0 ^b	154.1 $\pm$ 48.4
CvO ₂ pv	114.4 $\pm$ 7.3	60.0 $\pm$ 7.5 ^{a,b,d}	105.9 $\pm$ 7.6 ^c
CvO ₂ hv	81.7 $\pm$ 20.0	26.8 $\pm$ 3.9 ^{a,b,d}	55.8 $\pm$ 15.5 ^{a,c,d}
DO ₂ th	122.6 $\pm$ 11.4	39.0 $\pm$ 6.6 ^{a,b,d}	63.3 $\pm$ 11.0 ^{b,b}
$\dot{V}O_{2$ th	150.6 $\pm$ 27.9 ^a	89.7 $\pm$ 17.9 ^b	117.3 $\pm$ 14.6
DO ₂ $\div$ $\dot{V}O_2$	98.9 $\pm$ 29.7	47.9 $\pm$ 8.0 ^{a,b,d}	60.0 $\pm$ 11.2 ^{a,c,d}
DO ₂ - $\dot{V}O_2$	108.4 $\pm$ 38.2	14.4 $\pm$ 3.6 ^{a,b,d}	46.0 $\pm$ 20.1 ^a

See footnote to Table 1 for abbreviations.

^a*P* < 0.05 vs baseline values.

^b*P* < 0.05 vs fentanyl.

^c*P* < 0.05 vs halothane.

^d*P* < 0.05 vs corresponding value during Stage II.

receiving isoflurane during the third stage of experiments.

Correlations were found between PBF, HABF and THBF, on one hand, and MAP and CO, on the other hand, during halothane anesthesia (Table 4). The association between the main hemodynamic variables and variables characterizing hepatic blood supply were much weaker and inconsistent during anesthesia with isoflurane or fentanyl (Table 4).

The values of hepatic oxygen supply as well as hepatic oxygen content in hepatic venous blood correlated very well with the main hemodynamic variables (MAP and CO) and variables characterizing hepatic blood flow during halothane, and, to a much lesser extent, during anesthesia with isoflurane or fentanyl (Table 5).

Discussion

The main hemodynamic variables and determinants of hepatic oxygen supply at Stage I of observations (baseline values) were not significantly different between groups. Because the study was designed to compare responses to standard (similar) surgical stress during different anesthetics, a control group could not exist: from a humanitarian point of view it was impossible to provide severe surgical stress without anesthesia. As a result, all values observed during the

Figure 1. Main hemodynamic variables during surgical stress under anesthesia using fentanyl, halothane, and isoflurane. MAP, mean arterial pressure; CO, cardiac output; THBF, total hepatic blood flow. All values are expressed in percent of baseline (Stage I) values. a, $P < 0.05$ vs baseline values; b, $P < 0.05$ vs fentanyl; c, $P < 0.05$ vs halothane; d, $P < 0.05$ vs corresponding value during Stage II.

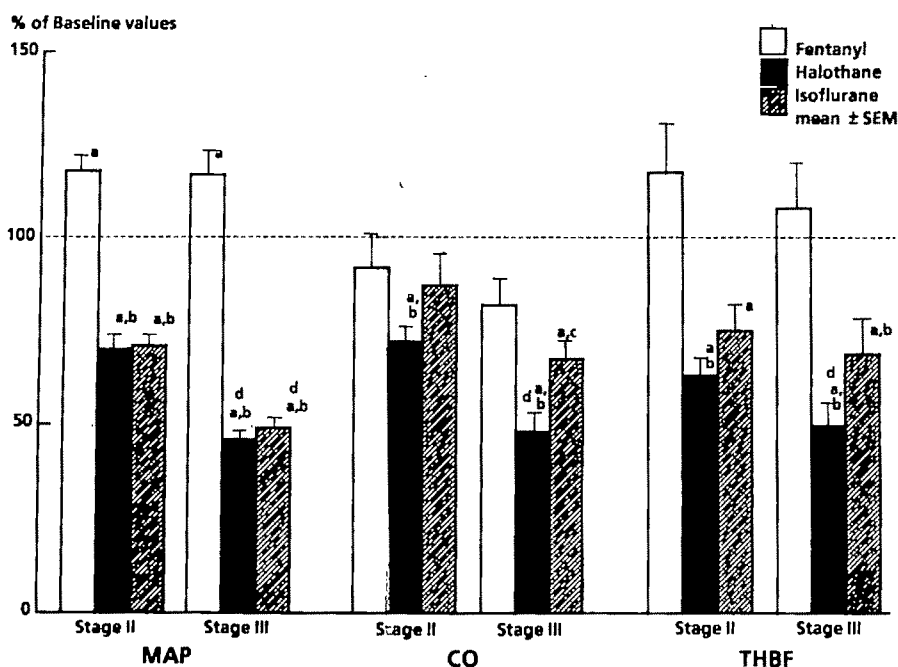
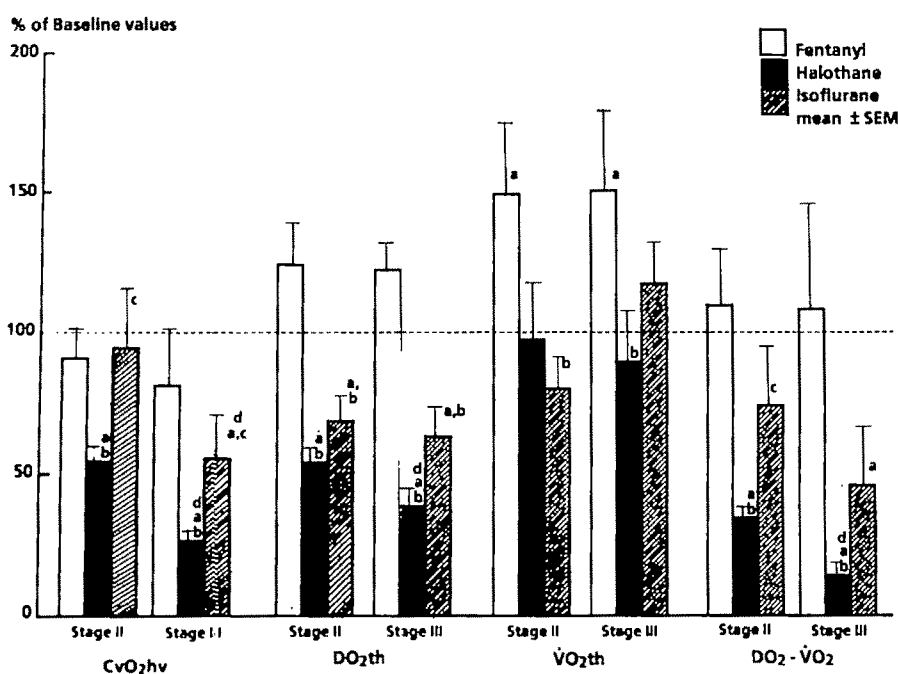


Figure 2. Hepatic oxygen supply/uptake relation during surgical stress and anesthesia using fentanyl, halothane, and isoflurane. $C_{vO_2}hv$, oxygen content in hepatic venous blood; DO_{2th} , $\dot{V}O_{2th}$, hepatic oxygen delivery, hepatic oxygen uptake, respectively; $DO_2 - \dot{V}O_2$, hepatic oxygen supply/uptake gradient. All values are expressed in percent of baseline (Stage I) values. a, $P < 0.05$ vs baseline values; b, $P < 0.05$ vs fentanyl; c, $P < 0.05$ vs halothane; d, $P < 0.05$ vs corresponding value during Stage II.



administration of different doses of studied drugs are compared with corresponding values observed during barbiturate anesthesia and the same surgical stress (Stage I).

Surgical Stress

Surgical stress such as laparotomy induces hepatic circulatory disorders (8,9), but the factors responsible

for such disorders have not been directly studied. Traction and manipulations on the viscera probably play a role; however, a general biological response to stress is also important. Laparotomy causes marked mesenteric vasoconstriction and a decrease in gastrointestinal blood flow that can be abolished by hypophysectomy (15). Surgical stress is usually accompanied by the release of various hormones and substances (including catecholamines, renin-angi-

Table 4. Coefficients of Correlation Between Systemic and Hepatic Hemodynamic Variables (Mean $\pm$ SEM)

	MAP			CO		
	Fentanyl	Halothane	Isoflurane	Fentanyl	Halothane	Isoflurane
PBF	0.79 ^a	0.71 ^a	0.12	0.59 ^a	0.73 ^a	0.18
HABF	-0.03	0.72 ^a	0.60 ^a	-0.03	0.82 ^a	0.57 ^a
THBF	0.53	0.75 ^a	0.45 ^a	0.38	0.82 ^a	0.46 ^a

Abbreviations: MAP, mean arterial pressure in mm Hg; CO, cardiac output in L/min; PBF, HABF, THBF, portal blood flow, hepatic arterial blood flow, total hepatic blood flow in ml·min⁻¹·g⁻¹, respectively.

^aP < 0.05.

Table 5. Coefficients of Correlation Between Variables Characterizing Hepatic Oxygen Supply and Systemic and Hepatic Circulation (Mean $\pm$ SEM)

	CvO ₂ hv			Do ₂ th		
	Fentanyl	Halothane	Isoflurane	Fentanyl	Halothane	Isoflurane
MAP	0.15	0.89 ^a	0.50 ^a	0.46	0.82 ^a	0.47 ^a
CO	0.46	0.89 ^a	0.46 ^a	0.31	0.88 ^a	0.46 ^a
PBF	0.34	0.74 ^a	0.16	0.58 ^a	0.84 ^a	0.77 ^a
HABF	0.38	0.89 ^a	0.65 ^a	0.67 ^a	0.95 ^a	0.92 ^a
THBF	0.53 ^a	0.86 ^a	0.50 ^a	0.92 ^a	0.95 ^a	0.97 ^a

Abbreviations: CvO₂hv, oxygen content in portal venous blood in ml O₂/dl; Do₂th, hepatic oxygen delivery in ml O₂·min⁻¹·g⁻¹; MAP, mean arterial pressure in mm Hg; CO, cardiac output in L/min; PBF, HABF, THBF, portal blood flow, hepatic arterial blood flow, total hepatic blood flow in ml·min⁻¹·g⁻¹, respectively.

^aP < 0.05.

otensin, vasopressin, etc.), which can and do disturb the splanchnic circulation. The concentrations of these circulating compounds are increased for much longer than several hours (16,17). Surgical preparation in this study consisted of laparotomy with rather dramatic manipulations on the liver and other intraabdominal organs, as well as thoracotomy. The effect of such extensive surgical preparation apparently lasted the entire experiment.

Halothane and Surgical Stress

In this study, extensive surgical trauma during halothane anesthesia was accompanied by the most severe disturbances in the hepatic circulation and the greatest reduction in hepatic oxygen supply. The majority of observations available in the literature show that halothane, in different species, is usually accompanied by greater hepatic circulatory disorders than are other inhalational anesthetics when surgery is not superimposed (1,18). However, such observations do not necessarily mean that an anesthetic administered during surgery is associated with hepatic circulatory disturbances similar to those observed during the same halothane anesthesia without surgical stress. In studies where laparotomy was performed, hepatic arterial blood flow usually decreased (6,19,20). On the other hand, in experiments where laparotomy was not employed, hepatic arterial blood flow increased or re-

mained unchanged, provided blood pressure and/or cardiac output was maintained at a minimum of 70% of baseline value (1,2,21-23). This point illustrates that responses of hepatic circulation observed during halothane anesthesia without surgery can be, and really are, very different from the responses observed during and immediately after surgery and the same anesthesia (1,18). From a clinical standpoint, knowledge regarding any dysfunction occurring during the combination of anesthesia and surgery is equally important to that during anesthesia alone. This study demonstrates that the combination of halothane anesthesia and surgical stress is associated with the lowest hepatic oxygen supply and hepatic oxygen supply/uptake ratio compared with the two other anesthetics studied.

Isoflurane and Surgical Stress

In some studies using dogs (2), pigs (24), and rats (3), isoflurane was associated with increases in HABF (in some studies statistically significant, in other studies substantial but statistically insignificant). In this study, HABF decreased during isoflurane anesthesia in a dose-related fashion to approximately the same extent it decreased during halothane anesthesia, although without a statistically significant difference between groups. The reason for the difference between this finding and the reports of the effects of anesthetics

on HABF reported previously is probably related to the surgical stress employed in this study, but not in others. The degrees of arterial hypotension during isoflurane anesthesia in our pigs and in swine in the study by Lundeen et al. (24) are not the same but are compatible: a 25% decrease in MAP in Lundeen's study vs a 30% decrease in our study at Stage II; and a 50% decrease in MAP in our study vs a 41% decrease in MAP in Lundeen's study at the last stage of observation. This hypotension was accompanied by compatible reductions in cardiac output (13 in our study vs 19% in Lundeen's study during Stage II, and a 32 vs 29% reduction during the last stage of observation in our study vs Lundeen's study, respectively). However, these relatively compatible changes in the main hemodynamic variables were accompanied by very different alterations in HABF: in our study HABF decreased to 58 and 40% of control values during Stages II and III, respectively, whereas in the study by Lundeen et al. it increased to 182 and 147% of baseline (awake) values during the second and third stages, respectively. Thus the combination of surgical stress and isoflurane anesthesia has a very different effect on hepatic circulation than does isoflurane anesthesia alone. It seems unlikely that differences in species play a significant role in this discrepancy because contrary to the observations in this study, in other studies on pigs (24) and dogs (2), HABF increased when surgical stress was not superimposed. This means that in dogs, as well as in pigs, when surgical stress is not included, HABF increases, whereas when the anesthetic is started in conditions of surgical stress, HABF decreases. It seems conceivable that in this study the probable decrease in PBF during laparotomy (9) by itself led to an increase in HABF (25,26). Then, isoflurane applied later decreased HABF from an already increased level.

Fentanyl and Surgical Stress

In isolated intestinal loop preparations in which perfusion pressure was maintained, fentanyl induced a dose-related vasodilation and a decrease in oxygen uptake, most likely resulting from a decrease in oxygen requirement (5). Considering that a decrease in PBF is directly related to a decrease in perfusion pressure, CO, or both (2,27,28), we hypothesized that fentanyl, providing a remarkably stable cardiovascular function (7), would also maintain hepatic blood and oxygen supply. To a certain extent, this hypothesis is confirmed by the present study: HABF and PBF, as well as THBF were very well maintained, if not increased (the difference did not reach a statistically significant level) during both doses of fentanyl

studied (Tables 2 and 3). However, the experiments also demonstrated that hepatic oxygen uptake during fentanyl administration increased significantly. This was not observed during inhalation anesthesia with either anesthetic. These changes in hepatic oxygen supply and uptake resulted in a well maintained, but unimproved (as we hoped) hepatic oxygen supply/uptake relation. The reasons for the increase in hepatic oxygen uptake during fentanyl administration are not clear. It seems conceivable that the dissipating effect of methohexital, in conjunction with the continued stress response, increased the metabolism within the liver, yielding a subsequent increase in hepatic oxygen demand. This increase in demand (followed by an increase in supply) was not blocked by fentanyl, but was substantially modified by isoflurane, as well as halothane. Further studies are required to test this hypothesis.

In conclusion, changes in HABF, PBF, as well as THBF, during halothane anesthesia and surgical stress are more closely associated with changes in MAP and CO than they are during similar stress and anesthesia with isoflurane or fentanyl. Hepatic oxygen supply depends on the two major systemic hemodynamic variables (MAP and CO) and hepatic blood flow during all three types of anesthesia. Hepatic oxygen uptake is maintained during inhalation anesthesia by an increase in oxygen extraction, whereas in animals anesthetized with fentanyl, an increase in oxygen uptake (due perhaps to increased oxygen requirement) is maintained by an increase in hepatic oxygen supply.

Our main hypothesis, that similar surgical stress with different anesthetics is accompanied by different degrees in hepatic circulatory disturbances as well as in the hepatic oxygen supply/uptake relation, is confirmed. During surgical stress, the 30% reduction in MAP induced by isoflurane is not associated with a deterioration in hepatic oxygen supply, whereas a similar degree of hypotension achieved by halothane decreases the hepatic oxygen supply and supply/uptake ratio. Our other hypothesis is only partially confirmed: fentanyl does maintain hepatic oxygen supply at baseline levels or higher, but because hepatic oxygen requirement is increased during fentanyl administration, the hepatic oxygen supply/uptake ratio is maintained, not increased, during fentanyl anesthesia. Thus, regarding the hepatic oxygen supply/uptake relation, halothane is less desirable than isoflurane or fentanyl anesthesia.

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Midazolam Antagonizes the Analgesic Effect of Morphine in Rats

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DAGHERO AM,, BRADLEY EL, KISSIN I. Midazolam antagonizes the analgesic effect of morphine in rats. *Anesth Analg* 1987;66:944-7.

The effect of midazolam on morphine analgesia was studied in 54 rats. Analgesia was determined by measuring threshold for motor response to noxious pressure applied to the tail. Midazolam (0.5 mg/kg) decreased the morphine-induced (1 mg/kg) increase in the reaction threshold by one-

half. Flumazenil (Ro 15-1788), a specific antagonist of benzodiazepines, prevented inhibition of morphine antinociception by midazolam. These findings demonstrate that midazolam partially antagonizes the analgesic effect of morphine and, in addition, that the antagonism of midazolam on morphine analgesia is mediated by benzodiazepine receptors.

Key Words: ANALGESICS—morphine. HYPNOTICS, BENZODIAZEPINES—midazolam.

The effect of benzodiazepines, primarily diazepam, on morphine analgesia has been investigated in humans and in animals, but the data are contradictory. Some investigators observed that benzodiazepines augment the analgesic effect of morphine in surgical patients (1-3); others have not (4-6). Indeed, the effect of diazepam on the pain threshold in surgical patients was found to be variable both in the direction of the changes and in their timing (7). The results of the studies on interaction between benzodiazepines and opioid agents performed in animals are as contradictory as those obtained in patients: diazepam has been found to decrease (8-10), increase (11,12), or have no effect (13) on morphine analgesia. Benzodiazepines exert their central effects via GABAergic mechanisms that appear to be involved in antinociceptive processes. However, the reported data on the effects of GABA agonists (GABA, muscimol, aminooxyacetic acid) on the analgesic action of morphine are complex. Generally, peripheral administration of GABA agonists increases the analgesic effect of morphine, but central administration inhibits this effect, suggesting that multiple interactions may occur (14).

The purpose of the present study was to investigate the effect of midazolam on the morphine-induced analgesia. In addition, the role of benzodiazepine receptors in the interaction of midazolam and morphine was evaluated with the use of the benzodiazepine receptor antagonist flumazenil (Ro 15-1788).

Methods

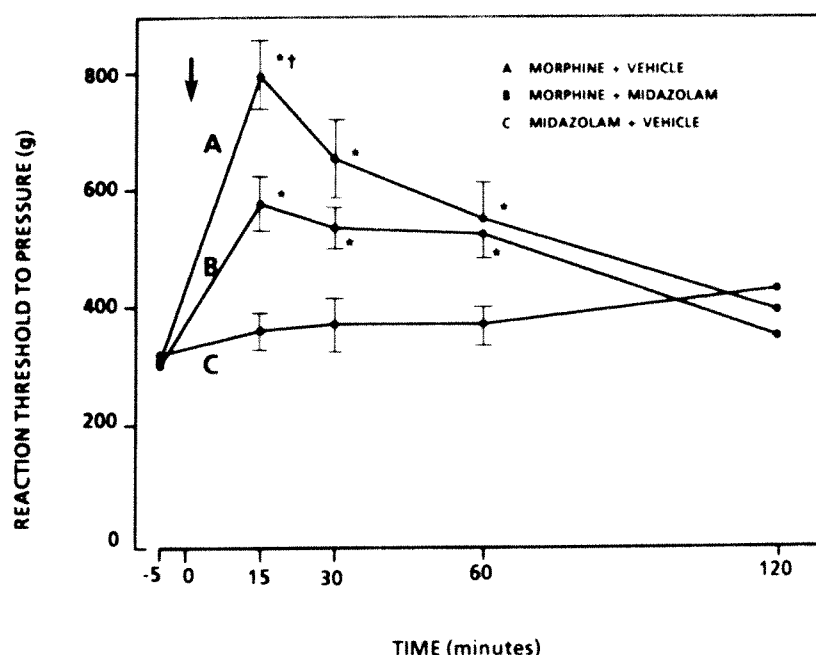
Experiments were performed on 54 male Sprague-Dawley rats weighing 325-400 g. The animals were housed in group cages in a large colony room. Food and water were continuously available. Each animal was used only once. All experiments were performed between 8:00 AM and 1:00 PM. Animal care standards in this study were in accordance with federal and institutional policy and the standards of the American Association for the Accreditation of Laboratory Animal Care as specified in the *Guide for the Care and Use of Laboratory Animals* (15).

Analgesia was determined by measuring the threshold of motor responses to noxious pressure applied to the tail using an Analgesy-Meter (Ugo Basile, Milan, Italy), a device that provides increasing pressure (16). The rat's tail was positioned on a Teflon platform, and the pressure plate (0.7 mm edge) attached to the device was placed 1-2 cm from the tip of the tail while the rat was held in the experimenter's hand. Pressure was increased at the constant rate of 64 g/sec until the animal made an attempt to escape (coordinated struggle). The pressure at that moment was recorded, and the mean of three consecutive measurements was taken as the individual reaction threshold. In each animal, the threshold was determined before and 15, 30, 60, and 120 min after administration of a drug (or the last component in a combination of agents). The following drugs were used: morphine sulfate (Lilly), midazolam hydrochloride (Roche), and flumazenil (Roche). Morphine was injected subcutaneously in a dose of 1 mg/kg, in a saline solution; midazolam, intraperitoneally, in a dose of 0.5 mg/kg in a saline solution; and flumazenil, intraperitoneally, in a dose of 10 mg/kg in a saline solution

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Figure 1. Effect of morphine sulfate, midazolam, and their combination on motor reaction threshold to noxious pressure. Ordinate: the reaction threshold in grams. Abscissa: time in minutes. Each line represents the mean $\pm$ SEM of determinations made in six rats. A, morphine (1 mg/kg); B, morphine-midazolam (1 and 0.5 mg/kg, respectively); C, midazolam (0.5 mg/kg). Arrow indicates the time of drug administration. Reaction thresholds at time -5 represents the baseline threshold. * Statistically significantly (Duncan's multiple range test, $P < 0.05$) different from midazolam group C. † Statistically significantly different from morphine-midazolam group B.



with the addition of Tween 80, 1 drop per 10 ml of saline. Doses of these drugs were chosen on the basis of preliminary experiments. Injection volumes ranged from 0.3 to 0.6 ml.

Two series of experiments were performed. In the first, the rats were randomly allocated to three groups of six animals each: morphine, morphine-midazolam, and midazolam. In the second series of experiments, the effect of flumazepil on the morphine-midazolam interaction was investigated; it consisted of the following four groups of nine animals (random allocation): morphine-flumazepil, morphine-midazolam, morphine-midazolam-flumazepil, and control (vehicles). Morphine, midazolam, and flumazepil were administered one after another at 1-min intervals. The results were evaluated statistically with the use of a one-way analysis of variance and Duncan's multiple range test at P value < 0.05 (17).

Results

Figure 1 shows the changes in reaction thresholds in the first series of experiments. Morphine, 1 mg/kg, caused a profound increase in the reaction threshold with the peak effect 15 min after its administration. Midazolam, 0.5 mg/kg, alone had no effect on the reaction threshold. When 1 mg/kg morphine was used in combination with 0.5 mg/kg midazolam the increase in the reaction threshold was statistically significantly less pronounced than that in the morphine group (800 ± 57 vs 579 ± 50 g, mean $\pm$ SEM). Com-

parison of the reaction thresholds in all three groups demonstrates that midazolam reduced morphine-induced analgesia by almost one-half.

Figure 2 illustrates the reaction threshold to noxious pressure 15 min after injection of the agents (peak action) in the second series of experiments. It shows that midazolam-induced decrease in the effect of morphine was eliminated by the benzodiazepine receptor antagonist flumazepil. The tendency for enhanced analgesia in the morphine-midazolam-flumazepil group was not statistically significant when compared with the morphine-flumazepil group.

Discussion

We have found that in rats midazolam antagonizes the analgesic effect of morphine. Antagonism between diazepam (as well as other benzodiazepines) and morphine has been reported in other experimental studies (8-10). However, some investigators have failed to find any reliable effect of diazepam on morphine analgesia (13), whereas two studies report that diazepam potentiates morphine analgesia (11,12). One reason for the inconsistent reports on analgesic interaction of benzodiazepines and morphine may be the different methods of testing for analgesia and methods for applying painful stimuli. The first indication that different types of painful stimulation may be differently influenced by agents used in anesthesia was reported in patients. Thiopental and Althesin, for example, decrease the pain threshold to pressure,

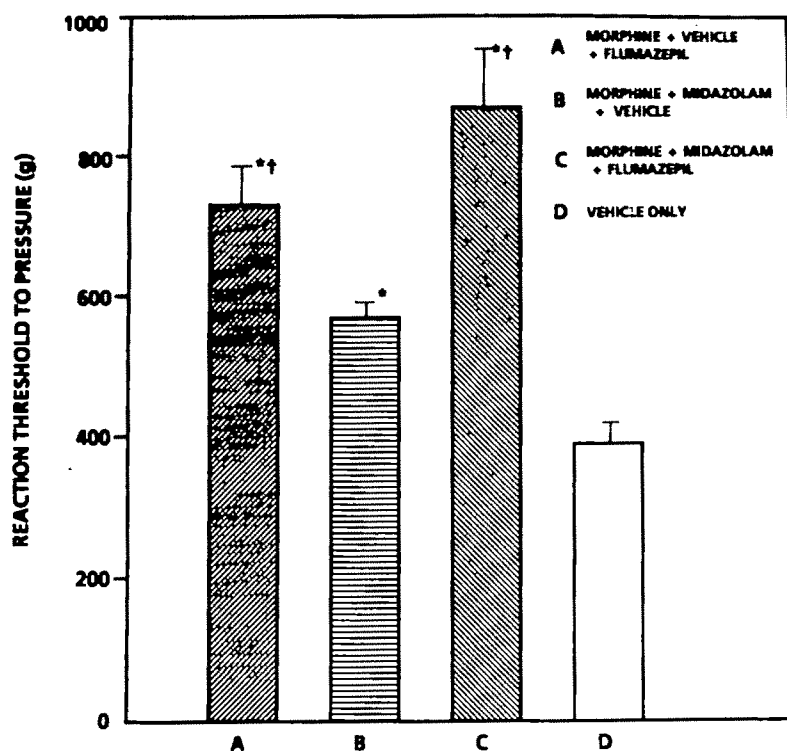


Figure 2. Effect of flumazepil (Ro 15-1788) on midazolam-morphine interaction. Ordinate: the reaction threshold in grams. On abscissa, each column represents the mean $\pm$ SEM of determinations made in a group of nine animals 15 min after the drug administration. A, morphine (1 mg/kg) and flumazepil (10 mg/kg); B, morphine (1 mg/kg) and midazolam (0.5 mg/kg); C, morphine (1 mg/kg), midazolam (0.5 mg/kg) and flumazepil (10 mg/kg); D, control (vehicles only). * Statistical significance (Duncan's multiple range test, $P < 0.05$) of the difference from control group D; † from morphine-midazolam group B.

but increase the thermal pain threshold (18,19). Similarly, it was found in rats that different opioid receptors are involved in mediating antinociceptive actions with different painful stimuli (20). For example, κ -opioid agonists are probably effective against somatic pain caused by mechanical stimulation and visceral pain caused by chemical stimulation, but not cutaneous pain caused by thermal stimulation (21). If different mechanisms are involved in the processing of different types of painful stimuli, outcome of an analgesic interaction between benzodiazepines and opioid drugs may depend on the type of noxious stimulation used.

Our data show that midazolam antagonizes the analgesic effect of morphine against pressure stimulation. This effect was similar to that of pentobarbital found in our previous experiments in rats (22). Data on the effects of benzodiazepines and barbiturates on pain have some similarity. For example, barbiturates (23) and benzodiazepines (3,24) moderate postoperative pain. Diazepam, when used intrathecally, has been shown to inhibit ascending activity evoked by stimulation of nociceptive afferent C fibers and non-nociceptive afferent A β -fibers (25); an effect similar to this was induced by intrathecal injection of pentobarbital (26). Much like pentobarbital, midazolam may provide an antinociceptive effect depending on the type of painful stimulation.

Benzodiazepines exert most of their central effect

by interaction with specific receptors that are part of the supramolecular GABA receptor complex (27). Flumazepil is a specific antagonist of benzodiazepine receptors (28). In the present study, flumazepil eliminated the morphine-midazolam antagonism, suggesting a receptor-mediated nature of the antianalgesic action of midazolam. Because midazolam is recommended for intravenous sedation and premedication (29), this ability might be important.

Evidence suggests that the mechanism of the antinociceptive effect of morphine is associated with activation of the descending inhibitory control systems (30-33). It is conceivable that midazolam, like barbiturates, inhibits the inhibitory control systems and, as a result, diminishes the effect of morphine.

Thus, our data indicate that midazolam can antagonize the analgesic effect of morphine. Although data from animal experiments and human clinical experience are difficult to correlate, it should be noted that pentobarbital-induced antagonism of morphine analgesia as measured by movement response to noxious pressure in rodents (22,34) is also present in human surgical patients (35,36).

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Lack of Size-Related Differential Sensitivity to Equilibrium Conduction Block among Mammalian Myelinated Axons Exposed to Lidocaine

B. Raymond Fink, MD, FFARCS and Andrew M. Cairns, PhD

FINK BR, CAIRNS AM. Lack of size-related differential sensitivity to equilibrium conduction block among mammalian axons exposed to lidocaine. *Anesth Analg* 1987;66:948-53.

This study sought to evaluate the sensitivity of individual, relatively thick myelinated axons of mammalian nerve to equilibrium conduction block by lidocaine, and to compare this to the incidence of conduction block previously measured in individual thinner myelinated axons. The incidence of conduction block by lidocaine 0.3 and 0.6 mM (8.1-16.2 mg/dl) was determined on 35 individual axons in dissected filaments of rabbit recurrent laryngeal nerve (RLN) in which the control conduction velocity ranged from 28 to 77 m/sec. Thirty-four axons (97%) remained excitable in lidocaine 0.3 mM; 2 axons (6%) remained excitable in lidocaine 0.6 mM.

These proportions did not differ significantly ($P > 0.2$) from those in thinner axons of vagus, either in comparisons with previous data from extracellular recordings or with new data from filament recordings. The results imply that differential blocks observed under clinical conditions probably depend on factors other than a size-related difference in the minimal equilibrium blocking concentration among myelinated axons. Equilibrium depression of the amplitude of RLN compound action potentials by lidocaine 0.3 and 0.6 mM was disproportionately great relative to the incidence of equilibrium conduction block in individual axons, confirming that depression of the compound action potential is not a reliable measure of nerve conduction block.

Key Words: ANESTHETICS, LOCAL—lidocaine. NERVE—differential sensitivity.

Differential nerve block is a commonplace accompaniment of clinical local anesthesia. One type occurs at the onset of plexus or nerve block (1), another persists throughout a spinal anesthetic (2), a third is observable to a varying degree for several hours with obstetric epidural block (3). Clinical differential nerve blocks consist of selective impairment or abolition of functional modalities, such as pinprick pain, vasoconstriction, and somatic muscle contraction. In vitro search for differential blocking properties of axons has led some workers to view thick (large, rapidly conducting) axons as intrinsically more resistant than thin (small, more slowly conducting) ones to conduction block by local anesthetic (4,5). Much of the supporting evidence comes from measurements of in vitro depression of compound action potentials (4,6). However, such depression does not necessarily reflect block

of conduction but can also arise from temporal dispersion; that is, from slowing of conduction in unblocked fibers (7,8).

Measurements with unit potentials avoid this particular difficulty but have yielded discordant results between amphibian and mammalian axons (5,9). It is clear that, at the unit level, differential time of onset of axonal conduction block is probably due not to differential sensitivity, but to difference in the distance between successive nodes of Ranvier. The large internodal distances in a thick myelinated fiber demand more time for the anesthetic to reach and block three successive nodes than do the smaller distances in a thin fiber (9). This differential disappears at equilibrium; unit studies on vagus nerve at equilibrium with anesthetic have indicated that the concentration that blocks mammalian myelinated axons is not a function of the axonal conduction velocity, and hence not a function of axonal size, although so far this demonstration has been restricted to mammalian fibers with conduction velocities below 27 m/sec (10,11). However, among amphibian axons, the blocking concentration of lidocaine has been reported to increase in direct proportion to fiber conduction velocity (5).

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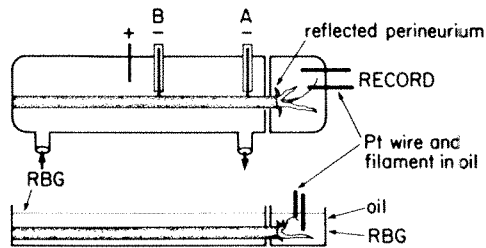


Figure 1. Schematic diagram of recurrent laryngeal nerve in exposure trough. Distances not to scale. Stimulation was applied at B or A in the perfused compartment at left. Distance from B to A, 20 mm; A to partition, 5 mm. Unit spikes were recorded via a platinum wire in a dissected filament immersed in mineral oil.

It therefore seemed desirable to evaluate further the relation of conduction blocking concentration to conduction velocity by studying rapidly conducting mammalian axons.

Methods

Rabbits were killed by intravenous injection of 1 ml thiopental sodium 2.5% followed by 30 ml air. Within 10 min the recurrent laryngeal nerves (RLN) and cervical portion of the vagus nerves distal to the nodose ganglion were excised and placed in perfusate solution.

The distal end of the nerve to be studied was desheathed under a dissecting microscope and teased into filaments. The perineurial sheath was otherwise retained intact. The nerve was then placed in a two-compartment trough, one compartment of which was perfused (Fig. 1). One of the filaments was lifted on a 0.5-mm diameter platinum wire into a thin layer of mineral oil floating on control solution in a well 2-mm deep. This wire served as a non-inverting recording electrode; the recording circuit was completed with an inverting electrode in the underlying solution. The perfused compartment was 40-mm long and held about 2 ml of solution that flowed through it at the rate of 6–10 ml/min. In this compartment the nerve rested against two bare-tipped monopolar insulated 0.13-mm diameter platinum wires B, A, 20 mm apart, either of which could be used as a stimulating cathode; electrode A was 5 mm from the partition. The stimulating circuit was completed by a bare platinum wire projecting into the perfusate. The filaments selected for study (one or two per nerve) each showed one or two clearly identifiable unit spikes. The conduction velocity (CV) of the axon was obtained from the difference in conduction times from B and A. The partition between the compartments was sealed with petrolatum.

The control perfusate contained (mmol/L) NaCl 120, CaCl₂ 2.2, MgCl 0.8, NaHCO₃ 16, glucose 20, equilibrated with 5% CO₂ - 95% O₂, pH 7.35–7.4, at 37–38°C.

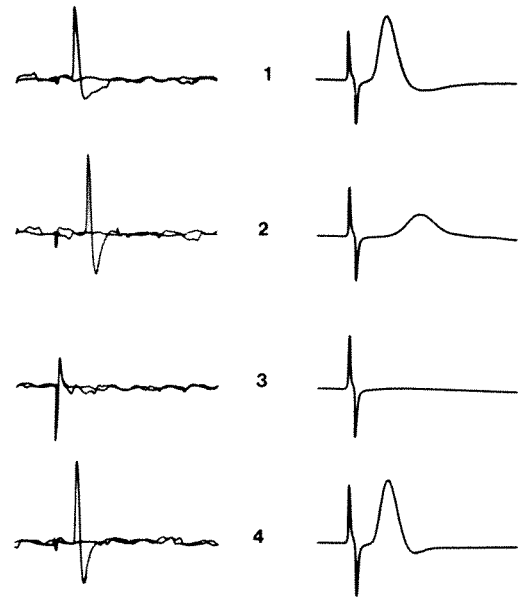


Figure 2. Unit and compound potentials from recurrent laryngeal nerve. The initial oscillation on the left of each trace is the stimulus artifact. Traces on left: unit responses from a filament; sweep width 9.9 ms. 1) Control; two sweeps, showing, respectively, response and failure of response to a 230- μ A 100 μ s threshold strength stimulus, indicating all-or-none character of the potential; spike amplitude 244 μ V, latency 0.925 ms, control conduction velocity 40 m/sec. 2) 20 min after onset of exposure to lidocaine 0.3 mM: response and failure of response to a threshold strength stimulus, now 900 μ A, 100 μ s. 3) 5 min after onset of exposure to lidocaine 0.6 mM: absence of response to two 5000- μ A 100 μ s shocks, indicating abolition of excitability; the stimulus artifact is exaggerated by the great strength of the stimulus. 4) 25 min after onset of wash: success and failure of response to threshold strength stimulus, now 350 μ A for 100 μ s, showing recovery to near control values. Traces on right: Compound potentials from a different nerve, with A- β deflection from large myelinated axons, sweep width 3.1 ms, amplifier gain 100, filter bandpass 10–10,000 Hz, stimulus 3 V $\times$ 100 μ s (2 $\times$ control supramaximal strength), conduction distance 20 mm. 1) Control; amplitude of A deflection 5640 μ V. 2) After 20 min exposure to lidocaine 0.3 mM; note increased latency and marked depression of the A component, under conditions that blocked very few units in filament recordings. 3) After 10 min in lidocaine 0.6 mM; note apparent total extinction, under conditions in which 2 of 35 filament units remained excitable. 4) After 20 min wash; amplitude of A component, 5490 μ V.

For testing the sensitivity of the studied unit to conduction block by lidocaine, perfusate contained in addition lidocaine 0.3 or 0.6 mM. These concentrations are respectively below and above previously determined ED₅₀ concentrations for conduction block of myelinated and unmyelinated axons of rabbit vagus nerve (10).

Conduction in units was tested with single 0.1–1.0-msec shocks of twice threshold strength (stimulator and stimulus isolation unit models 301-T and 305-2, WPI, New Haven, Connecticut). Responses were amplified by a WPI model DAM-5A differential preamplifier, gain 1000, bandpass 300–3000 Hz, displayed

Table 1. Incidence of Equilibrium Conduction Block by Lidocaine in Individual Myelinated Axons of Rabbit Vagus and Recurrent Laryngeal Nerve (RLN), in Successive Studies, 1982-1987

Year	Reference	Length of nerve in lidocaine (mm)	Number of axons	Number of axons blocked	Percentage blocked
Lidocaine 0.3 mM					
Vagus (ganglion recording)					
1982	10	23	23	2	13
1985	12	15	25	1	4
Vagus (filament recording)					
1985	12	25	16	0	0
1986	12	15	25	1	4
RLN (filament recording)					
1984	this paper	25	10	1	10
1985	this paper	25	25	1	4
Lidocaine 0.6 mM					
Vagus (ganglion recording)					
1982	10	40	4	3	75
1982	11	23	21	16	76 ^a
1985	12	15	22	11	50
1986	12	5	23	9	39
Vagus (filament recording)					
1987	this paper	25	12	10	83 ^{a,b,c}
RLN (filament recording)					
1984	this paper	25	10	9	90
1985	this paper	25	25	24	96 ^b

^a $\chi^2 = 0.22$, $P > 0.5$ (not significant).^b $\chi^2 = 1.63$, $P > 0.2$ (not significant).^cCV (m/sec) of individual axons = 37, 26, 24, 17, 15, 11, 10, 9, 7.6, 6.3, 6.0, 3.8 (*Italics indicate fibers not blocked by 0.6 mM lidocaine.*)

on a digital storage oscilloscope (model 4094, Nicolet, Madison, Wisconsin), recorded on magnetic disc, and transcribed on an X-Y plotter (model 17015B, Hewlett-Packard). Conduction velocity was initially tested with the nerve in control perfusate, using single shocks applied at the remote electrode B (Fig. 1) until the latency of the unit selected for study had remained stable for 60 min. The unit's control CV between B and A was then determined. Next, the perfusate was changed to solution containing 0.3 mM lidocaine HCl (8.1 mg/dl), circulated for 25-30 min, or until 2 min after the onset of conduction block tested from electrode B; this tested conduction in a 25-mm length of nerve exposed to anesthetic. In unextinguished units the increase in latency reached a plateau within 20 min in RLN and within 30 min in vagus nerve. If the unit was not extinguished, perfusion with solution containing lidocaine 0.6 mM (16.2 mg/dl) was instituted and maintained for 25-30 min or until 2 min after block. Perfusion with control solution was then reinstated and recovery of conduction observed (Fig. 2, left). Deterioration of a preparation was evidenced by a slow, approximately 5%/hr increase in control latency and gradual decrease in amplitude of the unit spike; in the experiments where ganglion recordings were used (10), control latency increase due to deterioration was slower, <3%/hr, and spike amplitude

was usually stable. The practical effect of this was that a given filament recording seldom exceeded 2 hr, in contrast with ganglion recordings, in which 6 hr studies were the rule. However, 23- and 25-mm lengths of vagus nerve exposed to drug showed almost identical incidences of block in the two systems (Table 1), notwithstanding that the two studies were separated by a span of 5 years.

To assess the respective roles of axonal conduction block and temporal dispersion in depression of the compound action potential of the whole nerve by anesthetic, compound potentials were recorded from seven other RLNs using a system (Fig. 3, top) described by Heavner and de Jong (6). In brief, supra-maximal stimulation was employed to test conduction of the compound action potential in nerve equilibrated successively with perfusate containing lidocaine 0, 0.3, 0.6 mM, and 0 mM. Temporal dispersion was further evaluated in two additional RLNs from the increase in latency and decrease in amplitude effected successively with lidocaine 0.3 mM, 10-mm increase in conduction distance, and cooling to 22°C. The χ^2 -test was used to evaluate the statistical significance of differences in the incidence of equilibrium block in RLN units and vagus axons. The t -test was used to statistically evaluate amplitude changes in compound action potentials.

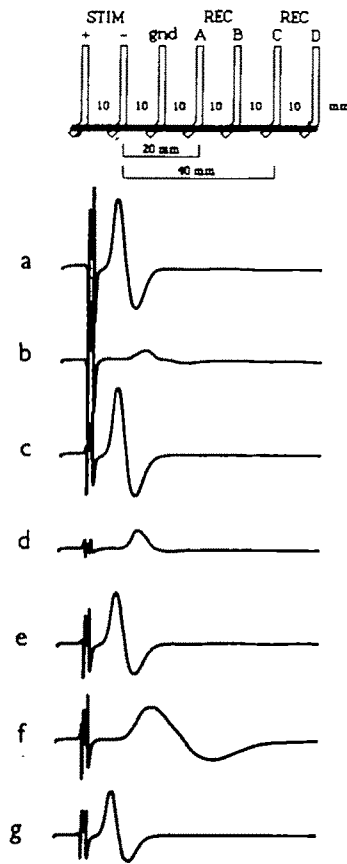


Figure 3. Compound action potentials of recurrent laryngeal nerve at equilibrium with superfusate. Sweep width, 5.0 ms. a) Control; spike amplitude, 1.925 mV; b) lidocaine 0.3 mM; c) wash; d) 10-mm increase of conduction distance; e) control conduction distance, ambient temperature 38°C; f) ambient temperature 22°C; g) ambient temperature 38°C.

Results

Data were obtained from a total of 35 individual myelinated fibers in 24 filaments of 18 recurrent laryngeal nerves, one nerve per rabbit. A typical set of observations is shown on the left in Figure 2. The control conduction velocity measured in the axons ranged from 28 to 77 m/sec and averaged 45 ± 12 m/sec (mean $\pm$ SD). Exposure to lidocaine 0.3 mM resulted in block of conduction in 2 of the 35 units; lidocaine 0.6 mM extinguished conduction in an additional 31 units (Table 1).

Comparison was made with the incidence of conduction block in vagus units recorded via the nodose ganglion in a previous report (Table 1, Ref. 11, CV 3.5–27 m/sec). A second comparison was made with the 12 units (mean CV 14.4 ± 10 m/sec) recorded in six filaments of three vagus nerves (one nerve per rabbit) treated with 0.6 mM lidocaine in the present

study; conduction block developed in 10 of these units. χ -square tests indicated that the differences between these groups were not statistically significant ($P > 0.2$) (Table 1).

The effect of lidocaine 0.3 and 0.6 mM on the A deflection of an RLN compound potential conducted over a length of 20 mm is illustrated on the right in Figure 2. In seven experiments on different nerves, lidocaine 0.3 mM depressed the A component to $33 \pm 7\%$ of the control amplitude and to $53\% \pm 9\%$ of the control area; these effects were more than 95% reversible. A perceptible C elevation was not present, the great majority of the fibers of this nerve being skeletal motor (13). Lidocaine 0.6 mM abolished the compound potential completely (Fig. 2).

The A fibers of the recurrent laryngeal are of course also contained in the cervical vagus, so it was predicted that the A β -component of the cervical vagus nerve potential would be depressed by lidocaine to about the same extent as that of the recurrent laryngeal, and this was indeed found to be the case: tested in five vagus nerves from these rabbits, lidocaine 0.3 mM depressed the A β -component to $37 \pm 9\%$ of control amplitude and $50 \pm 14\%$ of control area, neither of which differed significantly from the corresponding value for the recurrent laryngeal ($t = 0.877$, 0.503; $P > 0.1$).

Depression of a recurrent laryngeal nerve A potential by three different agencies, each involving temporal dispersion, is illustrated in Figure 3. The effect on amplitude and latency of the deflection was approximately the same whether caused by 0.3 mM lidocaine, cooling to 22°C, or a 10-mm increase in the conduction distance. Tested on a second nerve the effects were similar or more pronounced.

Discussion

With lidocaine 0.6 mM, the incidence of block in 25-mm lengths of RLN axons (filament recordings) was 90–96%. The Table offers two relevant comparisons: 1) with data from a previous study using ganglion recording, in which the incidence of block in a 23-mm length of vagus axon exposed to anesthetic was 76%, and 2) with data from the present filament recordings, in which the block incidence in a 25-mm length of axon exposed to anesthetic reached 83%. The difference between these incidences are not statistically significant. However, the possibility must be considered that thick fibers in the RLN deteriorated more rapidly than did thin ones in the vagus and, had they not done so, might have shown a lesser incidence of block than did the thin ones. Several comments are perti-

nent to this point. First, if decreasing conduction velocity (increasing latency) under control conditions may be used as an index of deterioration, the rate of deterioration during the control equilibration period was essentially similar in the RLN and vagus filament preparations. Second, the pattern of block in individual vagus axons randomly chosen, examined via filament recordings, argues against differential thickness-related deterioration. The CV values of the individual axons are listed in Table 1. The CV of the two fibers that escaped block in lidocaine 0.6 mM was 15 and 10 m/sec, whereas five slower (thinner) and four faster (thicker) axons did manifest conduction block. So that, in vagus, there was no indication of a greater selective deterioration among thicker fibers than among thinner ones, as well as no indication that thick vagal fibers were more resistant to block than were thin ones. Finally, observations with filament recordings were limited to 3 hr per nerve, versus 6 hr in ganglion recordings of previous studies. Thus, taken at face value, the data in Table 1, from mammalian axons, lead to rejection of the hypothesis that large myelinated axons (represented here by RLN axons, CV 28-77 m/sec) are less sensitive to conduction block by local anesthetic than are small myelinated axons (as represented here by two populations of vagus nerve axons, CV 3.5-27 and 3.8-37 m/sec, respectively).

Staiman and Seeman (5) however, as noted earlier, deduced a direct proportionality between the lidocaine concentration (0.1-1 mM) producing conduction block in individual axons and the conduction velocity (9-42 m/sec) of the axon. Their study employed tissue from a different class of animal (amphibian, bath temperature 22°C), collision technique, and relatively few axons (nine, only three of which were in the conduction velocity range studied here). The different conclusion may arise from any or all of these factors.

An important point demonstrated in Table 1 is that comparison of the incidences of conduction block in RLN and vagus units must take into account the length of nerve exposed to the drug. The length of vagus axon exposed to anesthetic in the ganglion recordings from previous studies ranged from 5 to 40 mm, and the incidence of block in such axons was an inverse function of the length of nerve in contact with the drug. This is easily reconciled with the established fact that block of three consecutive nodes, a distance of 2-6 mm, is all that is necessary for block of conduction in any given myelinated axon. A high probability of block of three consecutive nodes, however, requires the use of a relatively high concentration of anesthetic, several times larger than the ED₅₀ concen-

tration, which is about 0.4 mM lidocaine for vagus myelinated axons (10,11). With concentrations near the ED₅₀, a length of nerve greater than the minimum three-node length will have to be exposed to the drug to assure block. This is so because the probability of block may be assumed to differ from node to node, and one or more of the three consecutive nodes blocked with a higher concentration may not be sufficiently sensitive for all three to block with a low concentration. With any near-ED₅₀ concentration there will be a minimum length of drug-equilibrated nerve within which the probability of block of three consecutive nodes reaches a maximum. Data in Table 1 indicate that with lidocaine 0.6 mM this length was between 15 mm and about 23 mm in rabbit cervical vagus. Extrapolated to other nerves under clinical conditions, this has the practical implication that complete block of conduction in a nerve cannot be assured unless a local anesthetic concentration exceeding the minimum equilibrium blocking concentration (MEC) is present over a requisite length, which conceivably may reach several cm under unfavorable circumstances. With 1% lidocaine, the concentration injected is approximately 40 mM, or some 100 times that of MEC, but the size and persistence of the MEC zone will be a complicated function of anatomy, technique, and pharmacokinetics.

As regards the experimental observations on compound action potentials of RLN, these demonstrated a >50% depression of the compound A β -deflection by lidocaine 0.3 mM, whereas the corresponding units revealed only a 10% incidence of conduction block. This, apparently the first available direct comparison of its kind, indicates that a large part of the decrease in amplitude of the compound potential must have been due to temporal dispersion without block (Fig. 2), which also occurs with low temperature (7) (Fig. 3). Demonstration of the uncertain correlation between block of conduction in individual fibers and compound action potential depression by local anesthetic suggests that the effect of local anesthetic on the compound potential does not necessarily reflect conduction block, and would be more accurately described in terms of percent depression than percent block.

In conclusion, the results of this study do not support explanations of clinical differential block that rely on size-related differences in sensitivity to conduction block among myelinated axons. Unfortunately, definitive alternative explanations are not yet available (14).

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Toxicity of Chloroprocaine and Sodium Bisulfite on Human Neuroblastoma Cells

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SERAVALLI E, LEAR E. Toxicity of chloroprocaine and sodium bisulfite on human neuroblastoma cells. *Anesth Analg* 1987;66:954-8.

The effects of commercial and crystalline solutions of chloroprocaine (CP) (1.6×10^{-3} – 0.4×10^{-3} M) and sodium bisulfite (SB) (0.8×10^{-3} – 0.08×10^{-3} M) were studied on the multiplication of human neuroblastoma cells. These cells were chosen because of putative neurotoxicity associated with CP; cell multiplication (measured as colony-forming ability—CFA) was studied because CFA is a reliable in vitro test for drug toxicity at the cellular level. CFA was dramatically reduced (86%) after 20-hr exposure to commercial solutions of CP. Shorter exposure times (3 hr) re-

sulted in a marginal toxic effect (32%). At similar concentrations and after 20-hr exposure time, CP crystalline solutions induced a 37.5% inhibition that decreased with decreased time in culture. Sodium bisulfite reduced cell multiplication to a degree that varied with different samples of SB. With a 3-hr exposure time, CFA was reduced 72–92% by SB-1 and 57–72% by SB-2. The variability of SB toxicity and the difference in toxicity with commercial and crystalline solutions of CP are discussed in terms of possible clinical toxicity.

Key Words: ANESTHETICS, LOCAL—chloroprocaine. TOXICITY—chloroprocaine.

Several reports (1–4) have described neurologic complications in patients given chloroprocaine (CP) for epidural anesthesia. Initially, inadvertent intrathecal administration of CP in a concentration of 3% was thought to be the problem, but several studies in vivo (5,6) and in vitro (7) suggested a possible toxic effect of the drug in lower, clinically relevant concentrations. The problem has renewed interest in the toxicology of CP because its rapid hydrolysis was thought to assure minimal toxicity (8,9). Recently, Wang et al. (10) reported that sodium bisulfite (SB), the antioxidant present in the commercial solutions of CP, produced long lasting hind limb paralysis in rabbits in which commercial CP was injected into the subarachnoid space; crystalline CP, however, did not produce neurologic deficits.

Because little is known about the toxicity of SB on nerve cells, we have combined studies of neurotoxic effects of CP on a human neuroblastoma cell line with similar studies using SB. As an index of toxicity we used cell multiplication measured by the method of colony-forming ability (CFA). This method, a proven

in vitro test for drug toxicity (11), is based on the ability of single viable cells to multiply and form colonies once seeded in petri dishes and allowed to attach to the bottom of the dishes. The colonies can be counted within a few days from the time of seeding. The number of colonies per dish is proportional to the number of seeded cells that multiply. Injured cells either detach from the dish surface or remain attached without being able to multiply and form colonies.

Materials and Methods

Cells

Human neuroblastoma cells were grown and maintained in Dulbecco's modified Eagle's medium (DMEM) (Gibco, NY) supplemented with 10% fetal calf serum (FCS), 50 units/ml penicillin, and 50 μ /ml streptomycin (Gibco).

Drugs and Concentrations

Commercial solutions of chloroprocaine (Nesacaine-CE; Astra, Worcester, MA), crystalline chloroprocaine (Astra), sodium bisulfite from two commercial sources, henceforth identified as SB-1 and SB-2, were diluted in serum-free medium (DMEM—vide supra) to eliminate the risk of a possible absorption of the drugs to proteins. Dilutions were made as follows: CP was

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Table 1. Colony-Forming Ability of Neuroblastoma Cells Exposed to Crystalline or Commercial Solutions of Chloroprocaine

Anesthetics	Concentrations $\times 10^{-3}$ M	Percent colony inhibition ^a					
		3-hr exposure ^b			20-hr exposure ^b		
		3 days	6 days	9 days	3 days	6 days	9 days
Crystalline solutions of chloroprocaine	1.6	14.3	16.7	3.6	37.5	0	0
	0.8	0	0	0	42.5	0	0
	0.4	0	0	0	32.5	0	0
Commercial solutions of chloroprocaine	1.6	35.6	30.5	30.4	76.0	91.4	95.9
	0.8	21.8	25.0	12.6	55.9	76.0	80.1
	0.4	14.2	19.3	10.1	48.7	59.7	83.6

^aAgainst control values (cells exposed only to anesthetic diluent).^bDays in drug-free medium after chloroprocaine exposure.

diluted to concentrations ranging from 1.6×10^{-3} (toxic limit) to 0.4×10^{-3} M, and SB to concentrations ranging from 0.8×10^{-3} (toxic limit) to 0.08×10^{-3} M. The concentrations of both drugs were chosen within limits that approximate the concentrations achieved in clinical practice. Dilutions of all drugs were prepared immediately before addition to the cells to avoid alkaline hydrolysis of chloroprocaine. Individual cell cultures were exposed to drug dilutions at pH 7.4 for 3 or 20 hr. Control cultures consisted of cells exposed to drug diluent alone without the addition of CP or SB. They were treated under the same conditions as the experimental cultures.

Cell Viability

Cell viability by trypan blue dye exclusion test was done before the cells were seeded on petri dishes (12). With this method the nonviable cells stain blue and the viable cells remain colorless. In each experiment the percentage of live cells ranged between 95 and 99%.

Colony-Forming Ability (CFA)

Individual human neuroblastoma cells in suspension were seeded in petri dishes (2.5×10^5 cells/plate) and incubated overnight for cell attachment. The next day the medium of each plate was removed and replaced with the one containing the appropriate drug dilutions. In each experiment every dilution was tested in duplicate cultures; each experiment was repeated twice. Accordingly, four different cell cultures were tested per drug dilution. Control cultures were exposed to drug-free diluent and similarly treated. After 3- and 20-hr exposures, the medium with or without drug was discarded and fresh drug-free medium was added to experimental and control cultures. The cultures were left undisturbed at 37°C and 5% CO₂ for

3, 6, and 9 days. After 3, 6, or 9 days, control and experimental cultures were removed from the incubator, washed in saline solution and stained with Wright-Giemsa. The number of colonies (≥ 10 cells) per petri dish was counted and recorded under the microscope. Cell multiplication was measured by the number of colonies that developed in each experimental and untreated culture. Reduction of CFA was determined by expressing the number of colonies in drug-treated cultures as a percentage of the number of colonies in its control culture.

Percent Inhibition

$$= 100 - \frac{\text{Number of colonies in experimental cultures}}{\text{Number of colonies in control cultures}} \times 100.$$

Inhibition was considered definite when it was $\geq 25\%$. Student's *t*-test (two-tailed) was used for statistical analysis. *P* values < 0.05 were considered statistically significant.

Results

Chloroprocaine

The CFA of human neuroblastoma cells exposed to CP is reported in Table 1 as percentage of CFA in control cultures. The 3-hr exposure to crystalline CP solutions followed by a 3-day incubation in drug-free medium did not result in any inhibitory effect of CFA with any of the concentrations of CP tested. On the other hand, a 20-hr exposure followed by 3-day incubation in drug-free medium inhibited CFA with all concentrations of crystalline CP tested. CFA averaged 37.5% below CFA levels observed in cells exposed only to anesthetic diluent ($P < 0.05$). Increased incubation periods in drug-free medium (6 and 9 days) after 20-hr exposure to CP restored the CFA of the

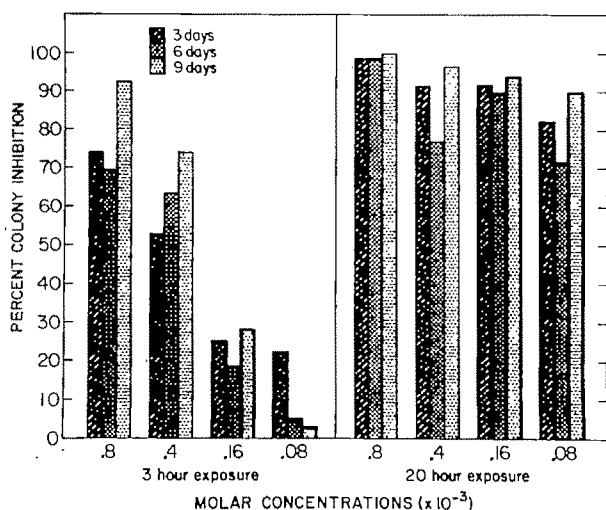


Figure 1. Effect of various molar concentrations of sodium bisulfite (SB-1) on the colony-forming ability (CFA) of human neuroblastoma cells. Single cells were exposed to SB for 3 and 20 hr, the number of colonies being counted after subsequent 3-, 6- or 9-day incubations in drug-free medium. CFA inhibition of drug-treated cultures was calculated as percentage of CFA in control cultures not exposed to SB-1 or SB-2.

cells, i.e., there was no difference in the number of colonies formed by control and experimental cultures (Table 1). In contrast to crystalline solutions, the $1.6 \times 10^{-3}\text{M}$ concentration of commercial solutions of CP proved toxic with both 3 and 20 hr of exposure. The 20-hr exposure produced an inhibition in the CFA (87%) that was greater than the 3-hr exposure (37.5%). In both exposure times, longer subsequent incubation times in drug-free medium did not restore the ability of the cells to multiply and form colonies. Lower concentrations (0.8×10^{-3} and $0.4 \times 10^{-3}\text{M}$) also inhibited the CFA of the cells, but only with prolonged exposure (20 hr) (Table 1).

Sodium Bisulfite

Sodium bisulfite had an inhibitory effect on CFA of neuroblastoma cells that varied with concentration and exposure time. In addition, SB toxicity also varied with the manufacturer's batches when tested under identical experimental conditions (Fig. 1 and 2). A 3-hr exposure time with $0.8 \times 10^{-3}\text{M}$ SB-1 inhibited CFA 72 to 92%, depending on the time of subsequent exposure to drug-free conditions (Fig. 1), whereas a 3-hr exposure time with $0.8 \times 10^{-3}\text{M}$ SB-2 inhibited CFA significantly less, 57 to 72%, $P < 0.005$ (Fig. 2). No difference in the inhibition of CFA was detected with SB-1 and SB-2 at concentrations below $0.8 \times 10^{-3}\text{M}$.

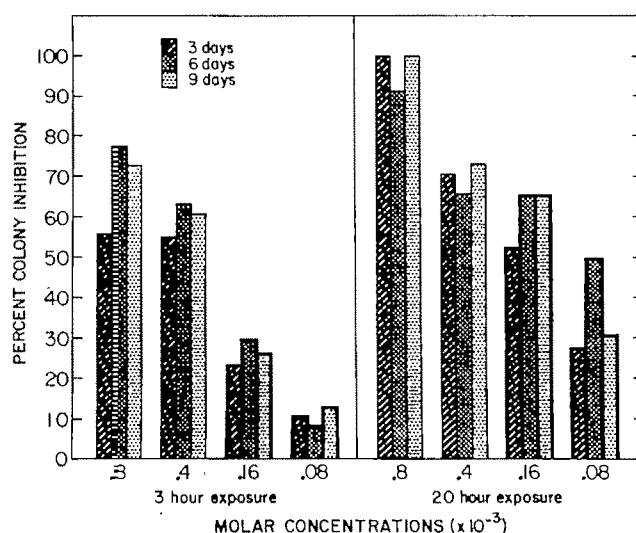


Figure 2. Effect of various molar concentrations of sodium bisulfite (SB-2) on the colony-forming ability (CFA) of human neuroblastoma cells. Single cells were exposed to SB for 3 and 20 hr, the number of colonies being counted after subsequent 3-, 6- or 9-day incubations in drug-free medium. CFA inhibition of drug-treated cultures was calculated as percentage of number of colonies in control cultures not exposed to SB-1 or SB-2.

In contrast to 3-hr exposures, CFA was equally (98%) inhibited in cells incubated for 20 hr in the presence of either SB solution ($0.8 \times 10^{-3}\text{M}$). At lower concentrations SB-1 appeared to be more inhibitory than SB-2. The CFA inhibitory effect of SB-2 was dose-dependent; that of SB-1 was not. Cells exposed to either sample of SB for 20 hr did not resume the ability to form colonies during the study period of 9 days (Fig. 1 and 2).

Discussion

The present data indicate that in human neuroblastoma cells exposed to crystalline solutions of CP for 20 hr, cell multiplication, as measured by CFA, was inhibited for only the first 3 days after exposure. Under the same experimental conditions, commercial solutions of CP induced an inhibition of cell multiplication that lasted throughout the study period (9 days). Viable cells of the type studied invariably proceeded to division; therefore, loss of colony-forming ability is a valid indication of cell toxicity.

The mechanism of inhibition of cell multiplication demonstrated by a reduction of CFA after exposure to anesthetics is not known. It is possible, however, that cells that do not form colonies may have been inhibited in their multiplication because of impaired DNA synthesis (13,14).

The inhibition of CFA by commercial solutions of

CP is in agreement with the findings of Sturrock and Nunn (15), who studied the effect of several local anesthetics on the CFA of a rodent cell line. They found that cell multiplication was inhibited by 24-hr exposures followed by 7-day incubation in anesthetic-free medium. Our data are also in agreement with the low systemic toxicity of the CP (8,9) because the reduction of cell multiplication after a 20-hr exposure to solutions of crystalline CP was only temporary.

In vitro CP is hydrolyzed at alkaline pH (15) to chloroaminobenzoic acid and diethylaminoethanol and the inhibition of cell multiplication raises the question of what effect these metabolites may have on cell metabolism and multiplication. The above two metabolites may have inhibited cell multiplication, but biotransformation of local anesthetic agents has been reported to be an insignificant factor in studies of cell cultures of this type (16). Thus, the finding that commercial solutions of CP that contain SB produced a toxic effect that prevented the cells from resuming normal multiplication during the study period (9 days) suggests that SB is a compound with potential mammalian toxicity. However, SB inhibited CFA of neuroblastoma cells to variable extents and the inhibition differed with different commercial samples of SB.

Low concentrations of sulphite (1 mM) have been reported to induce marked growth inhibition in mammalian cells (17). Although several mechanisms of toxicologic significance related to the autooxidation of sulphite have been suggested (18,19), studies with cell cultures have reported that irreversible reactions and free radicals produce chromosomal aberrations (19), alteration of the mitotic cycle (20), and damage of membranes with impairment of DNA synthesis (21). Whether a similar mechanism is involved in the inhibition of cell multiplication produced by commercial CP solutions remains to be elucidated.

Wang et al. (10) reported that SB from a single source and in concentrations similar to those used in humans induced chronic hind-limb paralysis in rabbits after subarachnoid injection. In their study, this effect was both dose-dependent and exposure time-related. This agrees with the inhibitory effect produced by SB in our in vitro experiments. Both the in vivo experiments by Wang et al. (10) and our in vitro study indicate that SB may have neurotoxicity of potential clinical significance.

The variable degree of toxicity among the SB samples in our study was not surprising because chemical compounds from different sources are recognized as having varying degrees of toxicity (22). In the case of compounds used in clinical practice, the variability of toxicity among samples may be important.

Although the in vitro toxicity of SB observed in the

present study cannot be extrapolated to clinical conditions in humans, the effect of SB on human nervous cell cultures reported here suggests that neurologic sequelae associated with CP in patients may be related to the toxicity of some samples of SB. If this is so, the reports of sporadic occurrences of neurologic sequelae in humans may be correlated with the differing grades of SB, as reported in our present study.

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End-Tidal PCO₂ Measurements Sampled at the Distal and Proximal Ends of the Endotracheal Tube in Infants and Children

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BADGWELL JM, MCLEOD ME, LERMAN J, CREIGHTON RE. End-tidal PCO₂ measurements sampled at the distal and proximal ends of the endotracheal tube in infants and children. *Anesth Analg* 1987;66:959-64.

To determine whether the site of gas sampling affects end-tidal gas measurements in pediatric patients, end-tidal PCO₂ was measured continuously from the distal and proximal ends of the endotracheal tube in 60 infants and children ventilated with an Air-Shields Ventimeter and a partial rebreathing circuit. These data were compared with simul-

taneous arterial PCO₂ measurements. In infants and children weighing ≥ 12 kg, both distal and proximal end-tidal PCO₂ values approximated arterial PCO₂ measurements. In infants and children weighing < 12 kg, however, only distal end-tidal PCO₂ measurements approximated arterial PCO₂ measurements. It is concluded that in infants and children weighing < 12 kg, accurate end-tidal measurements can be obtained only from the distal end of the endotracheal tube.

Key Words: ANESTHESIA—PEDIATRIC. VENTILATION—MECHANICAL.

Previous studies (1,2), correspondence (3), and a recent editorial (4) have alluded to the potential inaccuracies of measuring gas tensions in end-tidal gas samples in small infants and children. These inaccuracies may be attributed in part to the dilution of end-tidal gas with fresh gas as a result of placing the sampling catheter between the endotracheal tube and a partial rebreathing circuit (5). Such inaccuracies may lead to incorrect estimates of: 1) the adequacy of ventilation, 2) the alveolar-arterial relation of gases in the lung at equilibrium and, 3) the uptake and distribution of anesthetic gases. Several studies have avoided this problem by using anesthetic circuits with unidirectional valves (1,6,7), by sampling gas at the distal end of the endotracheal tube (7-10), or by sampling a single breath from the endotracheal tube when the fresh gas flow is discontinued (11). To determine the most accurate catheter position for continuous sampling of gas for measurement of end-tidal gas tensions in infants and children who are ventilated with a partial rebreathing circuit, we compared arterial PCO₂ (PaCO₂) with end-tidal PCO₂ (PETCO₂) measured in gas

sampled from the distal (PETCO₂-d) and proximal (PETCO₂-p) ends of the endotracheal tube.

Methods

After obtaining approval from our Committee on Human Research, we studied 50 unpremedicated healthy infants and children, ages newborn to 12 yr, ASA physical status I and II, who were scheduled for elective, nonthoracic, non-upper abdominal surgery. The patients had no known cardiopulmonary disease. All patients were studied in the supine horizontal position. After induction of anesthesia with thiopental (5 mg/kg), atropine (20 mcg/kg), and succinylcholine (1.5 mg/kg), the trachea was intubated with an endotracheal tube with no audible air leak at 30 cm H₂O. Ventilation was then controlled with an Air-Shields Ventimeter (ASV) and an Ayre's T-piece breathing circuit (Jackson-Rees modification). Anesthesia was maintained with 65% N₂O/35% O₂ and either halothane (0.5-1.5% inspired concentration), isoflurane (0.5-2.0% inspired concentration), and/or fentanyl (0.5-2.0 μ g/kg). All patients were paralyzed with either *d*-tubocurarine (0.4 mg/kg) or atracurium (0.4 mg/kg). Fresh gas flows, tidal volumes, peak inspiratory pressures, and respiratory rates were adjusted to maintain PETCO₂-d, PETCO₂-p, or PaCO₂ within the clinical range (26-44 mm Hg). Positive end-expiratory pressure (PEEP) was 0-2 cm H₂O. The study was commenced

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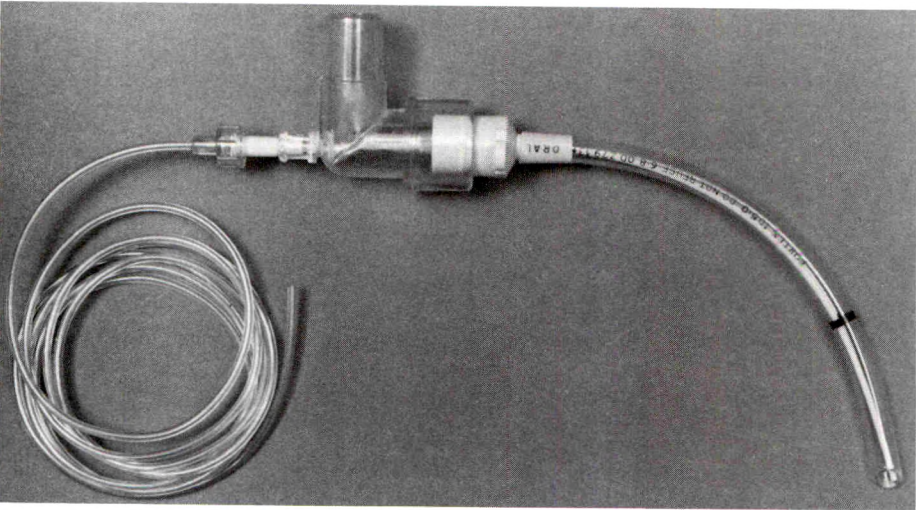


Figure 1. End-tidal PCO₂ is sampled from the distal end of the endotracheal tube through a 16-gauge Intracath catheter that was inserted into a clear plastic elbow with a central Luer-lok connection and attached to a 1.5-m sampling line from the CO₂ analyzer. (A 19-g Intracath catheter may be used for endotracheal tubes ≤ 3.0 mm OD.)

Table 1. End-Tidal PCO₂ Measurements Sampled at the Distal (PETCO₂-d) and Proximal (PETCO₂-p) Ends of the Endotracheal Tube in Infants and Children

	<12 kg		≥12 kg	
	(PETCO ₂ -d)	(PETCO ₂ -p)	(PETCO ₂ -d)	(PETCO ₂ -p)
Number of patients	25	22	24	19
Weight (kg)	7.2 ± 2.6 ^a	6.8 ± 2.4 ^a	21.8 ± 10.3	20.8 ± 10.2
ΔPCO ₂ (a-et) (mm Hg)	0.6 ± 2.0	8.7 ± 7.1 ^b	0.0 ± 1.7	0.9 ± 2.0
Number of patients with negative ΔPCO ₂ (a-et) values	8	1 ^c	13	4

Data are mean ± SD.
ΔPCO₂(a-et), the difference between PETCO₂ and (PaCO₂ values.
^aSignificant compared with the ≥12 kg groups.
^bSignificant compared with the other three groups.
^cSignificant compared with the PETCO₂-d groups.

after each infant or child was ventilated for no less than 15 min at the desired ventilator settings. Gas was continuously aspirated at 150 ml/min for measurement of the PCO₂ using a Puritan-Bennett infrared analyzer that was calibrated before each case. Gas from the distal end of the endotracheal tube was obtained through a #16 or #19 Deseret Intracath (#19 was used for endotracheal tubes ≤ 3.0 mm ID) inserted through a Luer-Lok connection in the elbow (12800, Dryden Corporation, Indianapolis, Indiana) of the anesthetic circuit to within 5 mm of the distal end of the endotracheal tube. The hub of the Intracath was then secured to the Luer-Lok connector of a 1.5-m sampling line (126671, Dryden Corporation) attached to the infrared analyzer (Fig. 1). PETCO₂-p measurements were obtained by sampling gas through a side-stream adaptor placed between the endotracheal tube and the breathing circuit. All PETCO₂ measurements were corrected for water vapor pressure, ambient barometric pressure, and N₂O. Arterial blood samples were obtained simultaneously with the end-

tidal measurements, analyzed with a PCO₂ electrode calibrated before each use, and corrected for body temperature. Whenever possible, both PETCO₂-d and PETCO₂-p were measured in the same patient. The PETCO₂-d and PETCO₂-p were measured within 15 min of each other during steady state.

After the study was completed, the patients were divided into four groups according to weight (less than or greater than 12 kg) and the sampling site (distal or proximal) for reasons given below, and in Table 1 and Figure 2. Differences in the mean weight and the arterial end-tidal PCO₂ difference [ΔPCO₂(a-et)] among the four groups were compared using one-way analysis of variance (ANOVA) and Student-Newman-Keuls test. The relation between ΔPCO₂(a-et) for distal and proximal values and weight was described by best-fit nonlinear regression analysis and the coefficient of determination (r²). The difference between PETCO₂-d and PETCO₂-p values [ΔPETCO₂(d-p)] were compared with body weight using best-fit nonlinear regression analysis and the coefficient of de-

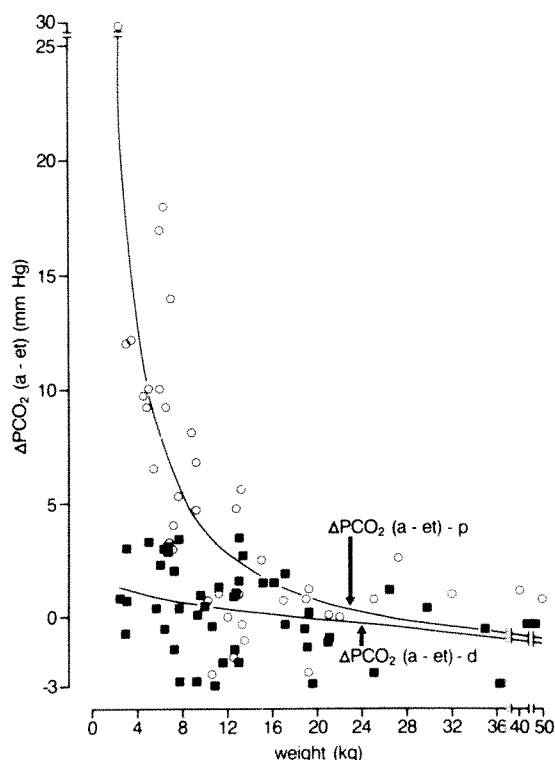


Figure 2. The gradient between arterial and end-tidal P_{CO_2} values [$\Delta PCO_2(a-et)$] compared with weight using sampling sites at the distal [$\Delta PCO_2(a-et)-d$] and proximal [$\Delta PCO_2(a-et)-p$] ends of the endotracheal tube. The slope for $\Delta PCO_2(a-et)-d$ is $y = -0.47x^{0.5} + 2$ with $r^2 = 0.10$. The slope for $\Delta PCO_2(a-et)-p$ is $y = 62.5x^{-1} - 2.3$ with $r^2 = 0.67$ ($P < 0.05$).

termination (r^2). The incidence of negative $\Delta PCO_2(a-et)$ values among the four groups were compared using Fisher's exact test. Statistical significance of $P \leq 0.05$ was accepted.

Results

Patients in the PET_{CO_2-d} and PET_{CO_2-p} groups did not differ significantly in weight (Table 1). Both PET_{CO_2-d} and PET_{CO_2-p} were compared with arterial values in 40 patients, PET_{CO_2-d} alone in an additional 9 patients, and PET_{CO_2-p} alone in one additional patient. Therefore, only one paired measurement (P_{aCO_2} vs PET_{CO_2-d} or PET_{CO_2-p}) was made in these additional 10 patients because of the limitation of time, the duration of surgery, or inability to obtain a second P_{aCO_2} sample. These 10 patients are included in the study because in each case the PET_{CO_2-d} or PET_{CO_2-p} is compared with the patient's own P_{aCO_2} value serving as a control.

Whereas there was no correlation between $\Delta PCO_2(a-et)$ and weight in the PET_{CO_2-d} groups, the $\Delta PCO_2(a-et)$ values in infants and children in the PET_{CO_2-p} groups

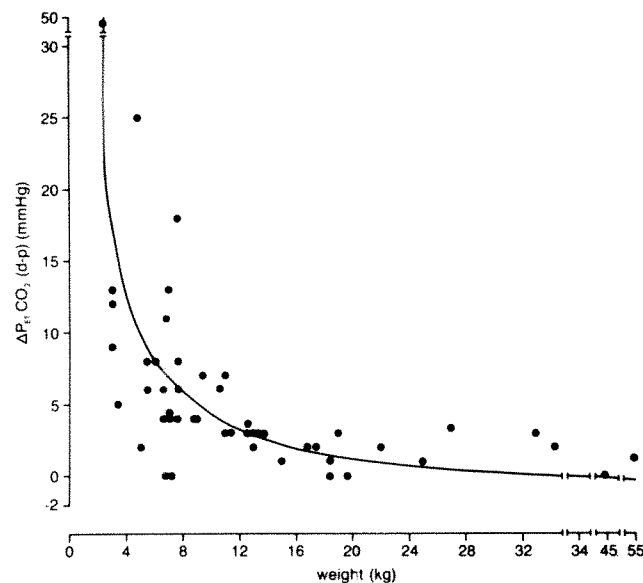


Figure 3. The gradient between end-tidal P_{CO_2} values sampled from the distal and proximal ends of the endotracheal tube [$\Delta PET_{CO_2}(d-p)$] in 49 patients compared with weight. Slope of the curve is $y = 58.8x^{-1} - 1.6$ and $r^2 = 0.49$ ($P < 0.05$).

increased as weight decreased below 12 kg ($P < 0.05$) (Fig. 2). Likewise, the $\Delta PET_{CO_2}(d-p)$ values increased as body weight decreased below 12 kg (Fig. 3). Using points on the horizontal segments of the hyperbolic curves where $\Delta PCO_2(a-et)$ and $\Delta PET_{CO_2}(d-p)$ values deviated from linearity, the patients were divided into groups of < 12 kg and ≥ 12 kg for further comparison. As a result of PET_{CO_2-p} measurements that consistently underestimated the P_{aCO_2} , the mean $\Delta PCO_2(a-et)$ value was significantly greater in the < 12 kg PET_{CO_2-p} group compared with the other three groups (Table 1).

In patients weighing < 12 kg, all capnographic waveforms from the distal sampling site showed uniformly constant plateau phases during expiration, whereas those from the proximal sampling site showed either failure to achieve plateaus (Fig. 4) or flat plateaus that underestimated the P_{aCO_2} (Fig. 5). In patients weighing ≥ 12 kg, the capnographic waveforms as seen in gas from the proximal sampling site showed flat plateaus with either the presence ($n = 13$) (Fig. 6) or absence ($n = 6$) of expiratory phase decay.

Capnography using distal sampling was helpful in the diagnosis of six potentially serious clinical situations that occurred during this study: endobronchial intubation (Fig. 7), kinked endotracheal tube (Fig. 8), partial reversal of neuromuscular blockade (Fig. 9), decreased pulmonary blood flow (Fig. 10), breathing circuit disconnections, and identification in one case of suspected malignant hyperthermia.

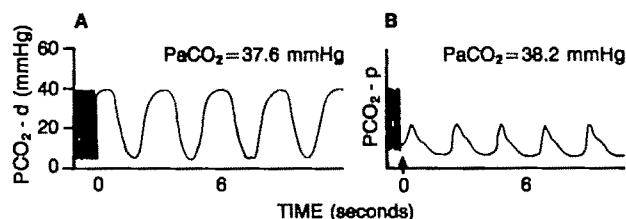


Figure 4. Capnographic waveforms obtained from the distal (A) and proximal (B) ends of the endotracheal tube in a 6.9-kg, 9-month-old infant. The changeover from distal to proximal sampling is indicated by the arrow. Fresh gas flow = 1.8 L/min, respiratory rate = 34 breaths/min, and peak airway pressure/positive end-expiratory pressure = 24/2.

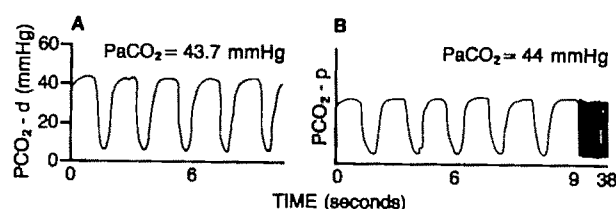


Figure 5. Capnographic waveforms obtained from the distal (A) and proximal (B) ends of the endotracheal tube in a 4.4-kg, 2-month-old infant. Fresh gas flow = 1.4 L/min, respiratory rate = 34 breaths/min, and peak airway pressure/positive end-expiratory pressure = 25/2.

Discussion

Distal sampling of respiratory gases in pediatric patients is not a new concept (7-10). The present study, however, compared the accuracy of distal and proximal measurements of respiratory gases *in vivo*. We found that PET_{CO_2-d} is the only reliable estimate of $PaCO_2$ in patients weighing < 12 kg who are ventilated with an ASV and a partial rebreathing circuit. In these patients, the PET_{CO_2-p} values consistently underestimate the $PaCO_2$ values, resulting in large $\Delta PCO_2(a-et)$ values. Therefore, in infants and children weighing < 12 kg, distal sampling is required for accurate PET_{CO_2} measurements. In contrast, both PET_{CO_2-d} and PET_{CO_2-p} provide reliable estimates of $PaCO_2$ in infants and children who weigh ≥ 12 kg.

In the < 12 kg group, the greater $\Delta PCO_2(a-et)$ values obtained by proximal sampling, compared with those obtained by distal sampling, are consistent with the hypothesis that gas sampled at the proximal site is a mixture of expired alveolar gas and fresh gas removed from the circuit by sampling. The increase in the $\Delta PCO_2(a-et)$ values as weight decreases below 12 kg is also consistent with this hypothesis. The amount of mixing depends on the ratio of expiratory flow rate to sample flow rate (5). In contrast, the smaller $\Delta PCO_2(a-et)$ values obtained by distal sampling, and the absence of a relation between weight and $\Delta PCO_2(a-et)$

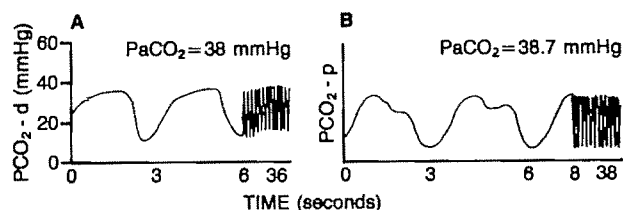


Figure 6. Capnographic waveforms obtained from the distal (A) and proximal (B) ends of the endotracheal tube in a 27-kg, 6-year-old child. End-tidal PCO_2 measurements were accurate despite an expiratory phase decay. Fresh gas flow = 3.7 L/min, respiratory rate = 13 cecay. Fresh gas flow = 3.7 L/min, respiratory rate = 18 breaths/min, and peak airway pressure/positive end-expiratory pressure = 20/2.

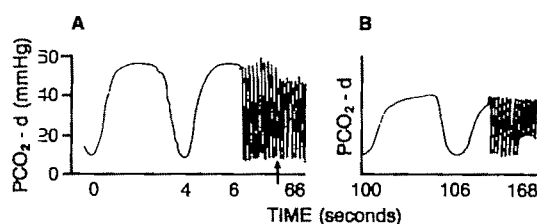


Figure 7. A) Capnographic waveforms obtained from the distal end of the endotracheal tube in an 18-kg, 4-year-old child with an endobronchial intubation. B) After diagnosis and correct placement of the endotracheal tube (denoted by the arrow in A), end-tidal PCO_2 returned to normal.

in the groups with distal PET_{CO_2-d} measurements, suggests that gas sampled at the distal sampling site is alveolar gas that is unaffected by the constant removal of 150 ml/min for sampling. Therefore, in infants weighing < 12 kg, ventilated with an ASV and partial rebreathing circuit, PET_{CO_2} values obtained from the distal end of the endotracheal tube reflect alveolar ventilation.

Although negative $\Delta PCO_2(a-et)$ gradients can be explained by the charged membrane theory (12) or by the delayed equilibration hypothesis (12), it is currently accepted that arterial and alveolar PCO_2 values are equal in the lung at equilibrium (13). Therefore, it is reasonable to assume that the distal PET_{CO_2} measurements do, in fact, reflect alveolar gas partial pressures. The small positive or negative $\Delta PCO_2(a-et)$ values in samples measured from the distal end of the endotracheal tube in all groups, and from the proximal end in the ≥ 12 kg group, may reflect either 1) calibration errors in the equipment, or 2) small ventilation-perfusion mismatches.

In addition to providing accurate quantitative measurements of PET_{CO_2} , distal gas sampling produces capnographic waveforms qualitatively superior to those obtained with proximal sampling. Accurate capnographic waveforms may aid the clinician in assessing the adequacy of ventilation and changes in the V_D/V_T

Figure 8. A) Capnographic waveforms obtained from the distal end of the endotracheal tube in a 7.5-kg, 6-month-old infant. The endotracheal tube was partially obstructed by a surgical mouth gag used during cleft palate repair. B) Before the diagnosis was made, end-tidal PCO_2 continued to rise despite an increase in the fresh gas flow. C) After diagnosis and relief of the obstruction, the patient was manually ventilated producing the capnographic waveform shown. D) Using controlled ventilation and the fresh-gas flows shown, the end-tidal PCO_2 and the capnographic waveform remained normal for the duration of the case.

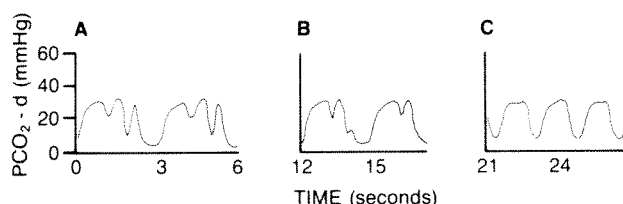
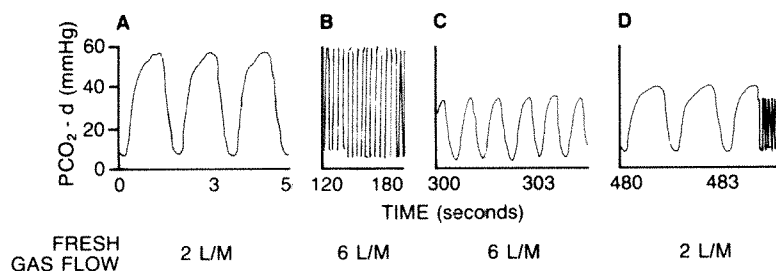


Figure 9. A) Capnographic waveforms obtained from the distal end of the endotracheal tube in a 5-kg, 4-month-old infant after partial recovery of neuromuscular function and attempts by the infant to breathe spontaneously. B, C) After increasing the inspired concentration of halothane from 0.5 to 1.0% and the respiratory rate from 18 to 36 breaths/min, the "curare cleft" resolved.

ratio (e.g., air embolism), verifying correct position of the endotracheal tube and its patency, and detecting breathing circuit disconnections. It may also be helpful in evaluation of neuromuscular blockade and in detection of low cardiac output (low pulmonary blood flow) states and malignant hyperthermia (14).

These data suggest that studies of the uptake and distribution of volatile anesthetics and MAC measurements in patients weighing < 12 kg using distal sampling of end-tidal gases (8-10) are more accurate than are studies that use proximal sampling (3,15). Errors of a magnitude similar to those found in this study may be anticipated if end-tidal gas is sampled from the proximal sites instead of the distal sites in patients weighing < 12 kg who are ventilated with a partial rebreathing circuit. The magnitude of the error will depend on the ratio of expiratory flow rate to sample flow rate (5). When high sample rates (≈ 150 ml/min) are used in small infants, the magnitude of the error will be great. The effects of other variables such as sampling tube length, sampling tube caliber, instrument response time, sample cell volume, respiratory rate, patient position, cardiothoracic disease, and type of surgery in pediatric patients remain to be determined.

In summary, we have determined that to obtain accurate end-tidal gas measurements with a partial rebreathing circuit in patients weighing < 12 kg, gas must be sampled from the distal end of the endotracheal tube, whereas in patients weighing 12 kg or

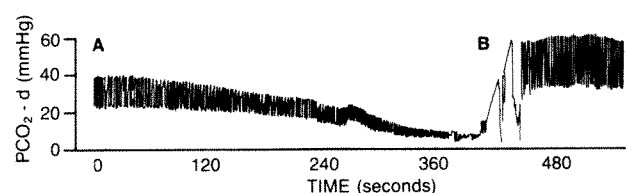


Figure 10. Capnographic waveforms obtained from the distal end of the endotracheal tube in a 10-kg, 1-yr-old infant with systemic hypotension that occurred during controlled ventilation with 2% halothane and 70% $\text{N}_2\text{O}/\text{O}_2$. A) The waveform shows a gradual but profound decrease in PET_{CO_2} , suggesting decreased pulmonary blood flow and carbon dioxide delivery to the lungs. B) Discontinuation of halothane and the administration of 100% O_2 was associated with a restoration of normal blood pressure and the return of end-tidal PCO_2 to above normal values.

greater, accurate end-tidal gas may be obtained from either the proximal or distal end.

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Spinal Anesthesia with Glucose-Free Bupivacaine: Effects of Age on Neural Blockade and Pharmacokinetics

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VEERING BTH, BURM AGL, VAN KLEEF JW, HENNIS PJ, SPIERDIJK J. Spinal anesthesia with glucose-free bupivacaine: effects of age on neural blockade and pharmacokinetics. *Anesth Analg* 1987;66:965-70.

Effects of age on spinal anesthesia using glucose-free 0.5% bupivacaine without epinephrine were studied in two groups of patients, one between 20 and 55 yr old, the other older than 55 yr. All patients received 15 mg bupivacaine. The time to onset of analgesia in caudad segments and the time to maximal motor blockade decreased with age. The upper level of analgesia did not change significantly with increas-

ing age. The times to recovery from analgesia at T12 and for the total disappearance of analgesia were longer in the older patient group. Effects of age on duration of motor blockade could not be demonstrated. Peak plasma concentrations of bupivacaine were significantly greater and the total plasma clearance significantly decreased in older patients. Age had no effect on time to peak concentration or the terminal half-life.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—effects of age. ANESTHETICS, LOCAL—bupivacaine. PHARMACOKINETICS—bupivacaine, effects of age.

Several factors may influence the distribution of glucose-free bupivacaine in cerebrospinal fluid (1-8). Age is one of them. The effects of age on dose requirement, time of onset of analgesia, level of analgesia, and duration of the blockade have been less often studied with spinal anesthesia than with epidural anesthesia. Moreover, discrepancies exist between the few studies of the effect of age on analgesic spread. Using glucose-free bupivacaine, some investigators found a more rapid onset and higher levels of analgesia with increasing age (9,10), whereas others found no correlation with age (8,11-13). Aging may also affect the pharmacokinetics of local anesthetics. For example, in a recent study we demonstrated that after epidural administration the terminal half-life of bupivacaine increased, whereas the total plasma clearance decreased with increasing age (14). Data after subarachnoid administration of bupivacaine are lacking.

In this study we investigated the effects of aging on both the quality and duration of spinal blockade as well as on the plasma concentration profiles after

subarachnoid administration of glucose-free bupivacaine.

Patients and Methods

After obtaining approval by the Committee on Medical Ethics of the University Hospital and informed consent, we studied two groups of patients (ASA status 1 or 2) scheduled for minor orthopedic, urological, or lower abdominal surgery. Patients in group 1 were 20-55 yr old; patients in group 2 were older than 55 yr (Table 1). None of the patients had a history of neurologic disease, hepatic disease, or bleeding diathesis.

Premedication consisted of lorazepam, 1-2 mg sublingually, 1.5 hr, and atropine, 0.25-0.5 mg IM, 45 min before induction of spinal anesthesia. A rapid intravenous infusion of 500 ml dextrose in saline was administered before the spinal injection. Thereafter the infusion rate was maintained at $2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. A central venous catheter was introduced into the superior vena cava via the basilic or the cephalic vein after local infiltration with lidocaine 0.5%, the catheter being advanced until the tip was located at least 6 cm proximal to the junction of the azygos vein and the superior vena cava. The correct location of the catheter tip was verified by X-ray film.

After local infiltration of the skin with lidocaine 0.5%, dural puncture was performed with a 25-g spinal

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Table 1. Patient Characteristics^a

	Group 1 (20-55 yr)	Group 2 (>55 yr)
Number of patients	14	15
Number of females	3	2
Age (yr)	34 ± 10	71 ± 8
Range	21-50	58-87
Weight (kg)	76 ± 10	75 ± 12
Range	52-100	57-95
Height (cm)	177 ± 7	172 ± 8
Range	165-193	165-188

^aData are mean ± SD

needle through an 18-g introducer, using a midline approach at the L3-4 interspace with the patient in the lateral position. The appearance of free-flowing clear cerebrospinal fluid (CSF) in the hub of the spinal needle indicated proper needle placement. Three milliliters glucose-free 0.5% bupivacaine (density at 37°C, 0.9993 g/ml) without epinephrine were injected in 30 sec without barbotage. After the injection the patient was immediately placed in the supine horizontal position. During surgery no sedatives were administered. Arterial blood pressure (sphygmomanometer) and heart rate (from the ECG) were monitored during anesthesia, during surgery, and in the recovery room. If the systolic blood pressure decreased >30% below preanesthetic levels or below 100 mm Hg, 5 mg ephedrine was given intravenously.

Analgesia was assessed and defined as absence of pain to pinprick. Motor blockade was evaluated bilaterally using a modified Bromage classification by asking the patient to raise the extended leg, flex the knee, and flex the ankle, and was rated per joint (0 = no, 1 = partial, and 2 = complete blockade). The results obtained in both extremities were added, giving a maximal score of 12 (complete motor blockade). Assessments were made every 5 min during the first 30 min after the injection, then at 15-min intervals until complete recovery. The following values were calculated:

- the time to initial onset of analgesia at the L1-2 dermatomes;
- the time to initial onset of motor blockade;
- the time to maximal cephalad spread of analgesia;
- the time to maximal caudad spread of analgesia;
- the highest level of analgesia;
- the maximal number of segments blocked;
- the maximal motor block score;
- the time until the level of analgesia had receded two segments;

the time until recovery of analgesia at the T12 dermatome;

the time until total disappearance of analgesia;

and the time until total recovery from motor blockade.

Central venous blood samples (5 ml) were collected before the spinal injection and at 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 90, 120, 150, 240, 360, 480, 600, 720, 960, 1200, and 1440 min after injection. Plasma was separated by centrifugation at 2,500 g, stored at -20°C, and assayed for bupivacaine using a capillary gas chromatographic method, as described by Burm et al. (15), with few modifications. After addition of an internal standard, the n-pentyl homologue of bupivacaine, 1 ml of plasma was extracted with 5 ml of n-pentane. The gas chromatograph (Hewlett-Packard 5710) was equipped with a fused silica column (length 10 m, internal diameter 0.32 mm, stationary phase [CP wax 57 CB]), a solid injection system, and a nitrogen-selective detector. The coefficient of variation was 15% at a bupivacaine plasma concentration of 1 ng/ml and <6% at plasma concentrations of 6 ng/ml and higher. Blank plasma samples of all patients were free from interfering substances. Also, co-administered drugs or their metabolites do not interfere with the assay of bupivacaine. The individual peak plasma concentrations (C_{max}) of bupivacaine, and the time at which these were reached (t_{max}) were determined. Terminal half-lives ($t_{1/2,z}$) were calculated from the rate constants (k_z) obtained by linear regression analysis of the log-linear part of the plasma concentration versus time curve.

$$t_{1/2,z} = 0.69/k_z.$$

The area under the plasma concentration-time curve (AUC) was determined using the linear trapezoidal rule, including extrapolation to infinity (16). The total plasma clearance (CL) was calculated according to the following equation:

$$CL = D/AUC,$$

where D is the administered dose.

Statistical comparisons were done using the Mann-Whitney U-test. The relation between variables of the neural blockade and age and between pharmacokinetic parameters and age were determined using linear regression and correlation analysis. A *P* value <0.05 was considered statistically significant. Values were expressed as mean ± SD, where appropriate.

Results

Satisfactory blockades were obtained in all patients. One young and two older patients were given atro-

Table 2. Characteristics of Neural Blockade after Subarachnoid Administration of Glucose-Free 0.5% Bupivacaine^a

	Group 1 (n = 14)	Group 2 (n = 15)
Analgesia		
Initial onset time (min)	3.9 ± 2.4	3.1 ± 2.2
Time to maximal cephalad spread (min)	18.2 ± 9.5	21.0 ± 6.8
Time to maximal caudad spread (min)	8.3 ± 6.5	4.0 ± 1.3 ^b
Maximal number of segments blocked	13.7 ± 2.8	15.2 ± 2.4
Highest level (T dermatome)	9.1 ± 2.8	7.7 ± 2.4
Duration highest level (min)	74.1 ± 29.7	69.2 ± 19.3
2-Segment regression (min)	99 ± 60	98 ± 18
Time to recovery at T12 (min)	99 ± 29	144 ± 39 ^b
Time to total recovery (min)	286.1 ± 72.1	374.5 ± 105.3 ^b
Motor blockade		
Initial onset time (min)	4.9 ± 4.0	3.4 ± 1.7
Time to maximal degree (min)	19.6 ± 10.8	11.6 ± 4.8 ^b
% Patients with complete block	100	100
Time to total recovery (min)	286 ± 75	320 ± 61

^aValues are mean ± SD^bDifferences between groups 1 and 2; $P < 0.02$.

pine within 20 min after administration of the local anesthetic because of bradycardia (heart rate <60 beats/min). Ephedrine 5 mg IV was given to two older patients when systolic blood pressure decreased more than 30% below the preanesthetic level. The mean decrease from control systolic and diastolic blood pressure during the first hour did not exceed 10% in both groups. Postspinal headache developed in two younger patients; one of these patients was treated with an epidural blood patch.

In all patients, bilaterally equal levels of analgesia were obtained: no patient developed a level of analgesia that varied more than one segment from the other side of the body. The characteristics of the neural blockade in both groups are summarized in Table 2. The time to maximal caudad spread was significantly less in older patients as were the times to onset of analgesia at L5 and sacral segments, especially at the S1-segment (Fig. 1).

There was no significant difference in the upper levels of analgesia in the two groups. Correlation analysis showed a statistically nonsignificant tendency for maximal height of analgesia to be higher in older patients ($r = 0.33$, $P = 0.07$, Fig. 2). A shortening of the time to initial onset of motor blockade could not be demonstrated. Complete motor blockade was obtained in all patients, but the time at which the maximal degree of motor blockade was attained was shorter in the older patient group. The times to recovery from analgesia at the level of T12 and for the total disappearance of analgesia were significantly longer in the older group. There was a moderate correlation between the time until total disappearance of analgesia and age ($r = 0.58$, $P = 0.008$, Fig. 3). An effect of age

on the recovery from motor blockade could not be demonstrated.

Figure 4 shows a representative example of plasma concentration versus time curves of an older and a younger patient. The results of the pharmacokinetic analysis are shown in Table 3. Peak plasma concentrations were significantly greater in the older patient group. However, times to peak concentrations were similar, as were the terminal half-lives. Total plasma clearance was significantly lower in the older patients. Also, there was a moderate inverse correlation between total plasma clearance and age ($r = -0.695$, $P = 0.00002$, Fig. 5).

Discussion

In this study age did not influence the upper level of analgesia. This is consistent with the results of Bengtsson et al. (8), Nightingale (11), Nolte and Stark (12), and Ryan et al. (13). On the other hand, Cameron et al. (9) and Pitkänen et al. (10) found a small but statistically significant correlation between age and the upper level of analgesia. It can be concluded that the clinical relevance of the effect of age on the maximal height of analgesia is marginal.

We demonstrated that the caudad spread of analgesia as well as the development of motor blockade occurs more rapidly in older patients. These effects are probably related to age-related changes in the central nervous system. With increasing age, peripheral nerves show a linear reduction in conduction velocity, especially in motor nerves. This slowing is believed to be secondary to axonal degeneration, a reduced number of nerve fibers and an increased mass of con-

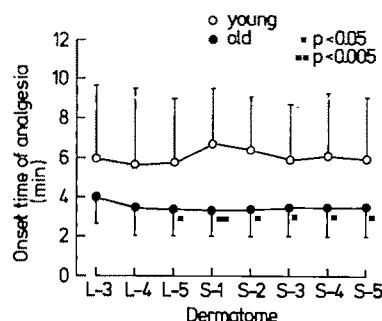


Figure 1. Mean onset times of analgesia at the caudal segments in the young and old patient groups after subarachnoid administration of glucose-free 0.5% bupivacaine.

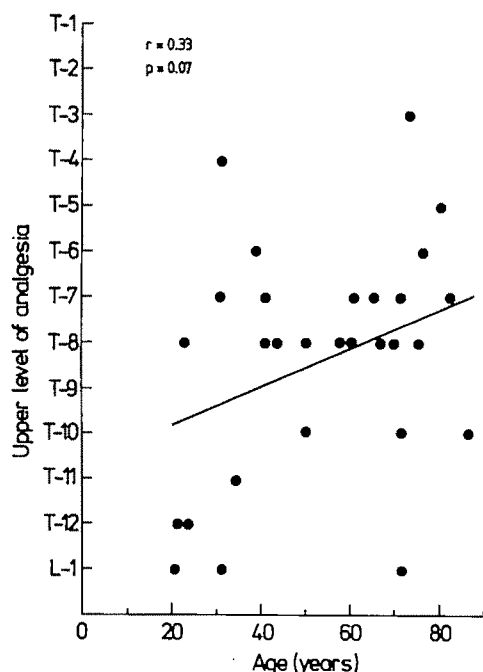


Figure 2. Relation between the upper level of analgesia and age after subarachnoid administration of glucose-free 0.5% bupivacaine.

nective tissue within peripheral pathways (17,18). Furthermore, in elderly patients the volume of CSF may be reduced (19), resulting in high CSF concentrations of the local anesthetic, which may contribute to the faster onset of analgesia and motor blockade.

It has been suggested that the duration of spinal anesthesia increases with age (20,21). In the present study we observed a statistically significant age-dependent prolongation of the duration of analgesia at T12 level and in lower segments, but no effect on the two-segment regression or the total duration of motor blockade. Our findings on motor blockade of the lower extremities are similar to the reports of most

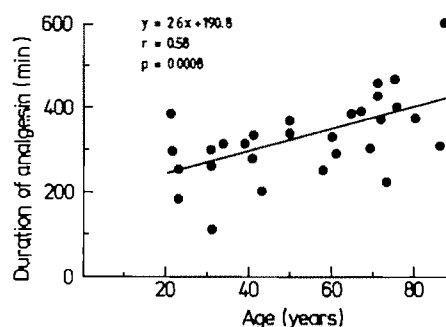


Figure 3. Relation between the time to total disappearance of analgesia and age after subarachnoid administration of glucose-free 0.5% bupivacaine.

of those authors who also administered 3 ml 0.5% glucose-free bupivacaine (1,2,6-8,10,22,23).

Plasma concentration curves of bupivacaine after subarachnoid administration were first described by Burm et al. (24), who investigated relatively young patients. Their results correspond with the values of the pharmacokinetic data of younger patients in the present investigation. Furthermore, our present results obtained in elderly patients are consistent with data recently reported by Axelsson et al. (25). The plasma concentration curves of bupivacaine after subarachnoid administration are characterized by low peak concentrations and relatively long peak times, which reflect a slow initial absorption rate (26).

The only data concerning the effect of age on the blood concentration of glucose-free bupivacaine have been reported by Pitkänen et al. (10). They observed no effect of age on the plasma concentrations. However, the sampling time in their study was too short (60 min) to obtain a complete blood concentration profile. Our data demonstrate a statistically significant but only moderate effect of age on the peak plasma concentration of bupivacaine, but no effect on the time to peak concentration. The higher peak plasma concentration in older patients may be due to an age-dependent speeding of the initial absorption rate of bupivacaine from the subarachnoid space into the general circulation or, more likely, to the marked decrease in the total plasma clearance. The terminal half-life of bupivacaine was not altered by age. It has been shown that the terminal half-life of bupivacaine with spinal anesthesia in younger patients (20-50 yr old) reflects a long absorption half-life, which characterizes a slow absorption phase (26). Therefore, it can be concluded that aging does not affect the slow absorption phase. This is consistent with the observation that the duration of the spinal anesthesia increases with increasing age. First, the amount of drug that reaches the sites of action may be greater in older

Figure 4. Representative plasma concentration profiles after subarachnoid administration of glucose-free 0.5% bupivacaine in a young and an old patient.

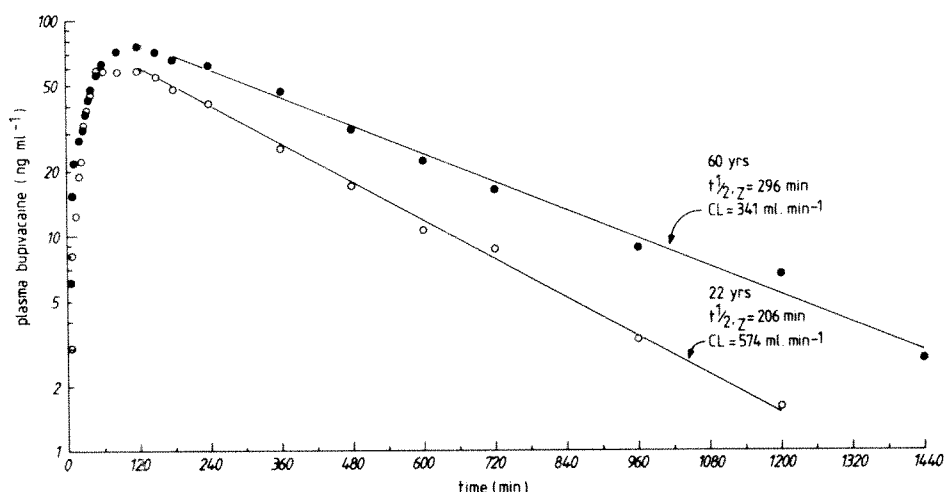


Table 3. Pharmacokinetic Data Obtained after Subarachnoid Administration of Glucose-Free 0.5% Bupivacaine^a

	Group 1 (n = 14)	Group 2 (n = 15)
t _{max} (min)	84 ± 53	105 ± 54
C _{max} (ng/ml)	75 ± 25	96 ± 23 ^b
t _{1/2,Z} (min)	288 ± 64	270 ± 93
CL (ml/min)	461 ± 94	284 ± 74 ^c

^aValues are mean ± SD.

^bDifferences between groups 1 and 2; *P* < 0.05.

^cDifferences between groups 1 and 2; *P* < 0.001.

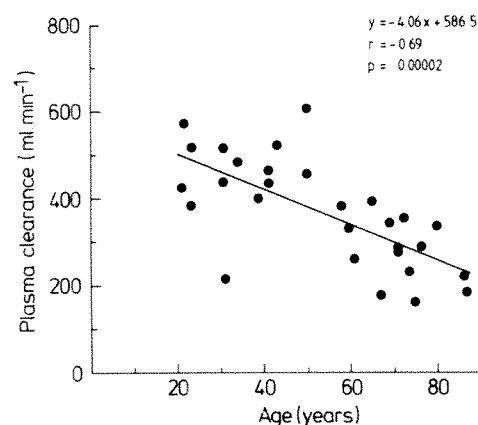


Figure 5. Relation between total plasma clearance of bupivacaine and age.

than in younger patients, so that even if the concentration at the sites of action decreases at the same rate, the absolute concentration at these sites is higher in older patients. Second, the increased duration of action in the older patients may be related to pharmacodynamic factors (age-related changes in the central nervous system) rather than pharmacokinetic factors.

In conclusion, with increasing age the duration of analgesia is prolonged in the elderly. In addition, aging is accompanied by increased plasma concentrations of bupivacaine and a marked reduction of the total plasma clearance of bupivacaine.

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Partition Coefficients of I-653 in Human Blood, Saline, and Olive Oil

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EGER EI II. Partition coefficients of I-653 in human blood, saline, and olive oil. *Anesth Analg* 1987; 66:971-3.

The purpose of this study was to determine partition coefficients for a new, inhaled anesthetic, I-653. Blood samples were taken from 11 patients scheduled for elective surgery who were ASA physical status I-III and ranged in age from 25 to 76 yr. At 37°C, we found a blood/gas partition coefficient of 0.424 ± 0.024 (mean $\pm$ SD); a saline/gas partition

coefficient of 0.225 ± 0.002 ; and an oil/gas partition coefficient of 18.7 ± 1.1 . These values indicate that I-653 will have a minimum alveolar concentration (MAC) required for anesthesia that is four to five times that of isoflurane and that I-653 will produce a rapid induction of and recovery from anesthesia.

Key Words: ANESTHETICS, VOLATILE—I-653. SOLUBILITY—I-653 partition coefficients.

Rapid recovery from anesthesia is an increasingly important goal of clinical practice, particularly for outpatient surgery. Although currently available potent inhaled anesthetics act rapidly and with minimal or no toxicity, recovery from the effects of these agents is still less rapid than might be desired. Consequently, interest has revived in the experimental inhaled anesthetic, sevoflurane (1), the low solubility of which (blood/gas partition coefficient of 0.59–0.69) (1,2) indicates a considerably more rapid recovery than that associated with the next least soluble anesthetic, isoflurane (blood/gas partition coefficient 1.4) (3).

However, sevoflurane appears to have limitations. It is metabolized (4) and unstable in the presence of soda lime (1,5). In addition, although it offers the advantage of low solubility, a still lower solubility seems possible. The partition coefficient of nitrous oxide, the least soluble of presently available inhaled anesthetics, is 0.47 (6).

I-653 is a new experimental inhaled anesthetic. Its MAC is slightly less than 6% in rats (unpublished data). It has the same structure as isoflurane except for the substitution of fluorine for chlorine on the α -carbon of the ethyl moiety. It is flammable at a concentration of 17% (unpublished data supplied by Ana-

quest). This compound has a relatively high vapor pressure (about 700 mm Hg at 22–23°C) (unpublished data). These properties indicate a lower solubility and greater stability than found with sevoflurane, and our initial studies have confirmed these differences (unpublished data). Recovery is extremely rapid with I-653, a finding also consistent with an agent having a very low solubility in blood (unpublished data). The role of the present study was to determine the solubility of this new agent in saline, oil, and human blood.

Methods

With approval from our Committee on Human Research and consent from each patient, we obtained 30 ml of venous blood from each of 11 patients ranging in age from 25 to 76 yr. All patients were ASA physical status I–III. There were four women and seven men.

The method of Lerman et al. (7–9) was used to determine the blood/gas and saline/gas partition coefficients of I-653. Fifteen-milliliter samples of blood or 0.9% saline were placed in 50-ml syringes and equilibrated by tonometry with 20 ml of 1.6–2.6% I-653 for 90 min in a waterbath at 37°C. The syringes were shaken vigorously every 15 min. The concentration of I-653 in the gas phase over each sample was determined by gas chromatography.

The oil/gas partition coefficient was obtained by the method described by Tanifuji et al. (10). Liquid I-653 (0.15 ml) was added to 100 ml of pure virgin olive oil and thoroughly mixed. Twelve milliliters of this mixture was equilibrated by tonometry with 20 ml of air

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for 15 hr in 50-ml syringes placed in a 37°C waterbath. The syringes were shaken vigorously once per hour for the last 4 hr of tonometry. The concentration of I-653 in the gas phase over the olive oil was then determined by gas chromatography.

For chromatography we used a 30-m, fused silica open tubular capillary (0.53-mm internal diameter) column coated with a layer of methylsilicone oil (J & W Scientific DB-1), which was 1.5- μ m thick. A nitrogen carrier stream of 6 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop.

After analysis of the gas phase in the syringes, aliquots of 10.069 ml of each of the equilibrated substances were transferred to 581-ml flasks. The blood and saline aliquots were transferred anaerobically to flasks from which a portion of the air had been evacuated to produce a negative pressure. The negative pressure drew the aliquot into the flask through a needle that pierced the Teflon stopper. A one-way stopcock was affixed to the needle. Each sealed flask containing blood or saline was placed in a 37°C water bath and shaken every 15 min for the ensuing 90 min, after which the concentration of I-653 was determined by gas chromatography.

Similarly, an aliquot (10.069 ml) of the equilibrated mixture of olive oil was placed in a 581-ml flask, but the aliquot was directly injected into the open flask. The flask then was sealed with a Teflon stopper pierced with a needle to which a one-way stopcock was affixed. The flask was equilibrated at 37°C and was shaken vigorously once an hour for 6 hr. After 6 hr, the concentration of I-653 in the gas above the mixture in the flask was determined by gas chromatography.

The partition coefficients (λ) were determined using the following equation:

$$\lambda = \frac{C_g(V_f/V_s)}{C_f - C_g}$$

where C_g is the concentration of I-653 in the gas phase in the 30-ml syringe used for tonometry; C_f is the concentration of I-653 in the gas phase of the flask; V_f is the volume of the flask; and V_s is the volume of the aliquot of blood, saline, or oil.

Dual determinations of the blood/gas partition coefficient were made for each patient. The paired values were averaged for each patient, and the averaged value assumed to represent the partition coefficient for that patient's blood. Averaged values for the partition coefficient were regressed against patient

age and hematocrit. Eight unpaired determinations were obtained for the saline/gas partition coefficient and seven unpaired determinations for the oil/gas partition coefficient.

Results

Patients' ages averaged 59.9 ± 15.4 (mean $\pm$ SD) yr. Hematocrit concentrations averaged $43.1 \pm 5.0\%$. The blood/gas partition coefficient was 0.424 ± 0.024 ; the saline/gas partition coefficient, 0.225 ± 0.002 ; and the oil/gas partition coefficient, 18.7 ± 1.1 . There was no significant correlation ($P > 0.05$) between patient age or hematocrit and the blood/gas partition coefficient, although the slope of the relationship between hematocrit and the blood/gas partition coefficient approached significance ($t = 1.90$; partition coefficient = $0.312 + 0.0026 \times$ hematocrit).

Discussion

The blood/gas partition coefficient of 0.424 suggests that I-653 will move into and out of the body as rapidly or more rapidly than nitrous oxide. Thus I-653 should anesthetize quickly and should permit prompt recovery from anesthesia. Our unpublished observations support the prediction of an extremely rapid rate of recovery, even from deep levels of anesthesia. These characteristics recommend its use for outpatient surgery, provided I-653 also possesses the attributes which make current, clinically applied inhaled agents safe and desirable to use. These properties include resistance to breakdown, minimal or absent toxicity, minimal or absent pungency, and a reasonable margin of safety. Resistance to breakdown is suggested by the similarity of the structure of I-653 to that of isoflurane and the known resistance of the latter to breakdown. Again, our unpublished data indicate that I-653 is resistant to breakdown and that this resistance appreciably exceeds that of any of the presently available potent inhaled anesthetics. The rapidity with which I-653 leaves the body should further reduce any possibility of breakdown and hence toxicity. These desirable properties may be counterbalanced by a predicted, clinically useful anesthetic concentration that is considerably higher than that required for anesthesia with currently used volatile anesthetics (see later). A higher concentration would increase the amount of agent available for biodegradation.

The blood/gas partition coefficient for I-653 was not significantly affected by hematocrit or patient age. However, the correlation with hematocrit approached significance, and a correlation such as increased sol-

ubility with increased hematocrit would be consistent with results reported for other inhaled agents in a previous study (9). The absence of a correlation with age distinguishes I-653 from other volatile inhaled anesthetics (8).

The product of MAC times the oil/gas partition coefficient equals a constant for most volatile anesthetics in humans (11). For isoflurane, the anesthetic structurally most similar to I-653, this product equals 104 (that is, $1.15\% \times 91$). Thus an oil/gas partition coefficient of 18.7 predicts an MAC for I-653 of 5.6%. As indicated earlier, unpublished data support this prediction for MAC. A MAC of 5.6% would be disadvantageous if, as appears likely, I-653 is an expensive anesthetic to manufacture. A closed system may be used for reasons of economy. The low solubility of I-653 may be a particular advantage in a closed system because, at a given alveolar concentration, the need to replenish the supply of anesthetic will be much less than that needed with any other potent inhaled anesthetic.

I-653 was donated by the manufacturer, Anaquest.

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MAC of I-653 in Rats, Including a Test of the Effect of Body Temperature and Anesthetic Duration

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EGER EI II, JOHNSON BH. MAC of I-653 in rats, including a test of the effect of body temperature and anesthetic duration. *Anesth Analg* 1987;66:974-6.

The anesthetic potency of a new fluorinated volatile anesthetic, I-653, was tested preliminary to testing its toxic and metabolic characteristics in rats. The minimum alveolar concentration (MAC) of I-653 at $37.9 \pm 0.2^\circ\text{C}$ (mean $\pm$ SD) in eight rats was $5.72 \pm 0.40\%$. In five rats, we reduced the rectal temperature to 28°C in two steps of 5°C . MAC

decreased by $0.238 \pm 0.036\%$ I-653 per degree centigrade decrease in temperature. That is, MAC decreased 42% as temperature decreased 10°C . We restored the temperature to 38°C and redetermined MAC. This value ($5.66 \pm 0.75\%$) did not differ from the average MAC obtained before hypothermia ($5.84 \pm 0.36\%$).

Key Words: ANESTHETICS, VOLATILE—I-653. POTENCY, ANESTHETIC—I-653.

I-653 is a new, volatile anesthetic whose molecular structure differs from that of isoflurane by substitution of a fluorine atom for the chlorine atom found on the α -ethyl carbon of isoflurane. This substitution markedly decreases the blood solubility of I-653 from that of isoflurane (blood/gas partition coefficients of 0.42 vs 1.41, respectively) (1,2), suggesting that the use of I-653 may be advantageous for procedures in which a rapid induction of and recovery from anesthesia are desirable. In the present study, we determined the anesthetic potency (MAC) of I-653 in rats, to provide a basis for future pharmacologic testing of the properties of this new agent.

Methods

Our study was approved by the UCSF Committee on Animal Research. Eight specific-pathogen-free, 2.5-month-old, male Sprague-Dawley rats weighing 381 ± 18 g were purchased from the Charles River Laboratories. Each animal was caged individually and had continuous access to standard rat chow and tap water before and after study.

The experiment was conducted as described previously (3,4) except that our limited supply of I-653

required the use of a closed anesthetic system. The Plexiglas cylinder (chamber) used to house the rats during their study (one rat at a time) had an internal diameter of 6.25 cm and a length of 29 cm. This diameter permitted the rat to crawl into the chamber, but prevented him from turning around.

Both ends of the chamber were equipped with rubber stoppers. The stopper at the "head" end of the chamber was traversed by three catheters: one for sampling, one for injection of I-653, and one for the delivery of oxygen. When not in use, the three catheters were sealed with stopcocks. The oxygen delivery catheter was connected to the stem of a T-tube, one arm of which was connected to an oxygen source and the other to a reservoir tube. During study, the oxygen bypass flow through the T was 500–600 ml/min. The head end of the chamber also contained a carbon dioxide absorber, charged for each study with 50–55 g of fresh, commercial (Sodasorb) soda lime. The absorber had walls of stainless steel mesh, and dust was cleared from the soda lime by flushing with a high flow of oxygen before beginning each study.

The stopper at the "tail" end of the chamber was pierced by a catheter, a hole for the tail, and a hole through which a small rectal temperature probe was passed. The catheter allowed us to flush oxygen through the tube prior to initiation of the study. It also was used to draw off gas when we wanted to introduce oxygen to lower the concentration of I-653. When not in use, it was sealed with a stopcock. The hole for the tail was large enough to allow passage of the tail snugly but without constriction.

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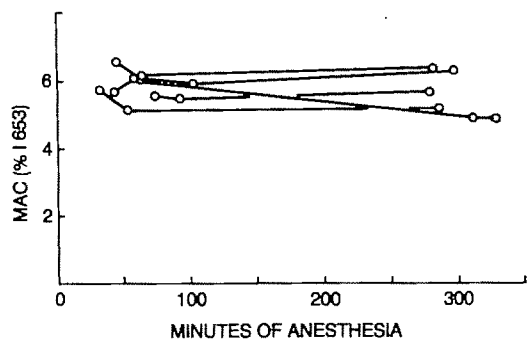


Figure 1. MAC for I-653 was measured immediately after induction of anesthesia and again after several hours. Hypothermia was imposed during the interval between these measurements, but the values shown in Figure 1 all were obtained in normothermic rats. These data indicate that MAC is unaffected by a duration of anesthesia of up to 5 hr. MAC for I-653 was $5.84 \pm 0.36\%$ before hypothermia and $5.66 \pm 0.67\%$ after hypothermia ($P = 0.63$ by paired analysis).

The rat was induced to enter the chamber. The rectal probe was inserted and secured to the tail with tape. The tail was pulled through the hole in the stopper which was then sealed with Dow Corning silicone stopcock grease. A 3–3.5 L/min flow of oxygen was directed through the chamber for 15 min, after which all openings to the chamber was sealed except for that to the oxygen bypass.

A gaseous mixture of I-653 was produced by adding 0.2–0.25 ml liquid I-653 to 20 ml of oxygen in a 100-ml glass syringe sealed with a stopcock. The evaporation of the I-653 rapidly increased the volume to about 70–75 ml. Anesthesia was rapidly induced in each rat by injection of 50–75 ml of this gas mixture. MAC was determined in duplicate in all eight rats. At least 15 min were allowed for equilibration at each step (concentration) used to bracket MAC.

I-653 was analyzed by gas chromatography. We used a Gow Mac Model 750 gas chromatograph equipped with a 30-m, fused silica open tubular capillary column (0.53 mm internal diameter) coated with a 5- μ m layer of methylsilicone oil (J & W Scientific DB-1). A nitrogen carrier stream of 6 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop.

The chromatograph was calibrated with a secondary tank standard that had been calibrated with a primary standard produced by injection of a liquid aliquot of I-653 into a flask of known volume. The determination of the primary standard required the determination of the specific gravity of I-653. Eight

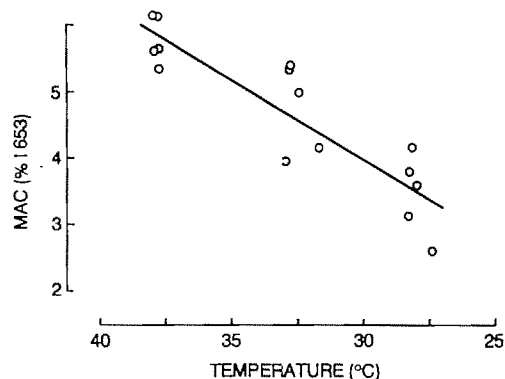


Figure 2. In contrast to the lack of an effect of duration of anesthesia, hypothermia decreased MAC. The decrease equalled $0.238 \pm 0.036\%$ I-653/°C and was highly significant ($P < 0.005$; $r^2 = 0.76$). The MAC for I-653 at 28°C was 58% of the MAC at 38°C.

determinations gave a value of 1.451 ± 0.003 g/ml at 22°C.

One problem with analysis was that the concentrations of I-653 required for anesthesia exceeded the linear range of our gas chromatograph. To reduce the concentration into the linear range we diluted each sample by at least a factor of 10. This dilution was accounted for in the calculation of concentration.

Five of the eight rats participated in a second phase of study. Immediately after the initial determination of MAC, we cooled each rat to approximately 33°C and then to 28°C. MAC was redetermined (single determination or "bracket") at each temperature step. Finally, the temperature was restored to 38°C, and MAC was determined once more (single bracket). Then, each rat was returned to his cage.

Data were translated into mean and standard deviation values. Regression analysis was applied to the temperature data using the averaged value at 38°C (both the values before and after the imposition of hypothermia were used to derive this value, and the value after hypothermia was weighted to give it parity with the values before hypothermia; that is, the single value after hypothermia was given the weight of two values so that it equalled the contribution of the two values obtained before hypothermia) for each rat and the values at 33°C and 28°C (thus, only three values for this determination were obtained from each rat). To determine whether MAC changed with increasing duration of anesthesia, a regression analysis also was applied to all data obtained at 38°C in the five rats tested for the effect of hypothermia. Finally, we used a paired *t*-test to determine whether the values obtained for MAC after hypothermia differed from those obtained before hypothermia.

Results

Injection of the mixture of I-653 and oxygen rapidly produced anesthesia. At the end of the study, each animal began to move within 1–2 min after departure from the chamber. All survived and appeared to be well 24 hr after anesthesia.

MAC for the eight rats before induction of hypothermia was $5.72 \pm 0.40\%$ I-653. The rectal temperature at these determinations was $37.9 \pm 0.2^\circ\text{C}$. For the five rats subjected to hypothermia, MAC before hypothermia was $5.84 \pm 0.36\%$ I-653 and $5.68 \pm 0.67\%$ after hypothermia ($P = 0.63$ by paired analysis). The values after hypothermia were obtained about 4 hr after the original values were obtained. No effect of increasing duration of anesthesia was found (Fig. 1). In contrast, hypothermia significantly decreased MAC (Fig. 2). The decrease equalled $0.238 \pm 0.036\%$ I-653/ $^\circ\text{C}$ ($P < 0.005$; $r^2 = 0.76$). The regression equation for the relationship of MAC to temperature was the following:

$$\text{MAC} = -3.16 + 0.238 \times \text{temperature}.$$

Thus MAC for I-653 at 28°C was 58% of MAC at 38°C .

Discussion

The potency of I-653 is greater than that indicated by its solubility in olive oil (1). In rodents, MAC times the oil/gas partition coefficient equals a value of approximately 200 for most volatile anesthetics (5), and thus an oil/gas partition coefficient of 18.7 would predict a MAC of over 9%. The lower-than-predicted value we obtained is unexplained, although it is notable that isoflurane, from which I-653 is derived, also

has a lower-than-predicted value. A MAC of slightly less than 4% I-653 might be expected in mature humans, because MAC for humans usually averages approximately two-thirds that in rodents (6).

The decrease in MAC with decreasing temperature is both qualitatively and quantitatively consistent with data from previous studies of potent volatile inhaled anesthetics. For both halothane and isoflurane, a 50% decrease occurs as core temperature decreases 10°C from normothermia (7). Similarly, the stability of MAC with increasing duration of anesthesia has been reported in several (8,9) but not all (4) studies.

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Rates of Awakening from Anesthesia with I-653, Halothane, Isoflurane, and Sevoflurane: A Test of the Effect of Anesthetic Concentration and Duration in Rats

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EGER EI II, JOHNSON BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: a test of the effect of anesthetic concentration and duration in rats. *Anesth Analg* 1987;66:977-82.

The low blood solubility of two new inhaled anesthetics, I-653 (human blood/gas partition coefficient, 0.42) and sevoflurane (0.69), suggested that awakening from these agents should be more rapid than awakening from currently available anesthetics such as isoflurane (1.4) and halothane (2.5). This prediction proved valid in a study of these four agents in rats given 0.4, 0.8, 1.2, or 1.6 MAC for 2.0 hr or 1.6

MAC for 0.5 or 1.0 hr. At a given dose and duration, awakening was most rapid with the least soluble agent and longest with the most soluble agent. For example, recovery of muscle coordination at 1.2 MAC administered for 2 hr required 4.7 ± 3.0 min (mean $\pm$ SD) with I-653, 14.2 ± 8.1 min with sevoflurane, 23.2 ± 7.6 min with isoflurane, and 47.2 ± 4.7 min with halothane.

Key Words: ANESTHETICS, VOLATILE—I-653, halothane, isoflurane, sevoflurane. RECOVERY—I-653, halothane, isoflurane, sevoflurane.

I-653 and sevoflurane are new, volatile anesthetics with blood/gas partition coefficients (0.42 and 0.69, respectively) that are appreciably lower than those of currently available anesthetics such as isoflurane (1.4) and halothane (2.5) (1-4). The lower solubilities should shorten the time to induction of and recovery from anesthesia with these new agents, a property that would be useful when rapid induction and recovery are desirable, as in outpatient anesthesia. To determine whether recovery was, in fact, more rapid with these two agents, we tested the times to awakening for all four anesthetics.

Materials and Methods

Animals

Our study was approved by the University of California, San Francisco Committee on Animal Welfare. Specific-pathogen-free, 3-month-old, male Sprague-Dawley rats weighing 270-340 g (at the time of study) were purchased from the Charles River Laboratories.

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Each was housed individually and had continuous access to standard rat chow and tap water before being studied.

Before being accepted for study, each rat passed a test of motor coordination (rotarod test) (5), requiring maintenance of position for 5 min on a rod 6 cm in diameter rotating at 8 rpm (Ugo Basile Rota-Rod Treadmill for Rats 7700). The test was performed twice before anesthesia: first, 1-3 days after arrival at UCSF, and second, within 2 hr before anesthesia. Each rat was given up to ten opportunities to pass the test at these trials. Rats failing the test (approximately five percent) were not used in the study.

Apparatus

Because we had a limited supply of I-653, we used a closed anesthetic system for all agents studied (Fig. 1.) The system was connected to a ventilator that alternately (20-30 times per minute) applied positive and negative pressure to a bag-in-box. The bag had a nominal volume of 500 ml. This arrangement provided the to-and-fro movement of gases in the system needed to eliminate carbon dioxide and to assure adequate mixing of anesthetic introduced into the system. Gas from the bag-in-box moved past an injection port and an oxygen inflow port (the latter used only before the start of each study to flush the system with

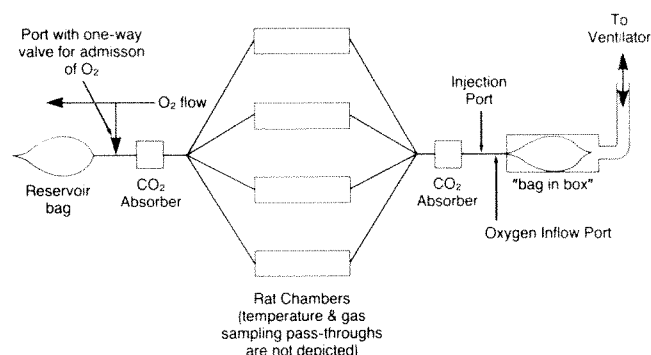


Figure 1. This schematic representation of the closed circuit used in the study is described in detail in the text.

oxygen) and through the first of two CO₂ absorbers. Anesthetics were injected through the injection port, as needed, to maintain the desired anesthetic concentrations. The port was sealed with a stopcock when not in use. The absorbers were charged for each study with 50–55 g of fresh, commercial (Sodasorb) soda lime containing 15 g water per 100 g soda lime. Blasts of air were used to clear dust from the soda lime prior to introducing the absorbers into the closed system.

The gas issuing from the first absorber was divided into four streams, each of which was directed to a chamber designed to contain a single rat. The ends of each chamber were sealed with rubber stoppers that had two openings or "pass throughs" (not shown in Fig. 1), one in the front for sampling gases (near the rat's head), and one at the rear for a rectal temperature probe. The sampling ports were sealed with stopcocks when not in use. All chambers were 27 cm long and had an internal diameter of 6.25 cm, which provided sufficient space for the rat to crawl into the chamber, but did not allow him to turn around.

The gases issuing from the rear of each of the four chambers were combined and directed through the second CO₂ absorber, then passed through a tube to a reservoir bag. The tube had a side port that permitted the addition of oxygen through a one-way valve from an oxygen delivery catheter. The oxygen delivery catheter was connected to the stem of a T-tube. One arm of the T was connected to an oxygen source and the other arm to a reservoir tube. During each study, the oxygen bypass flow through the reservoir arm of the T was 300 ml/min. Excess oxygen flow escaped through an underwater seal (1–3 cm water pressure).

To determine anesthetic concentrations, we used a Gow Mac Model 750 gas chromatograph equipped with a 30-m, fused silica open tubular capillary column (0.53- μ m internal diameter) coated with a 5- μ m-thick layer of methylsilicone oil (J & W Scientific DB-

Table 1. Anesthetic Concentrations and Durations Tested (+)

Duration (hr)	Anesthetic Concentration (MAC)			
	0.4	0.8	1.2	1.6
0.5	—	—	—	+
1.0	—	—	—	+
2.0	+	+	+	+

1). A nitrogen carrier stream of 6 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop. The chromatograph was calibrated with secondary tank standards that had been calibrated with primary standards produced by injection of a liquid aliquot of anesthetic into a flask of known volume. Because the concentrations of I-653 required for anesthesia exceeded the linear range of our gas chromatograph, we reduced the concentration into the linear range by diluting each sample by a factor of at least ten.

Protocol

After each rat was put in its chamber, the rectal probe was placed and secured with paper tape. A flow of 5 L/min or greater of oxygen was then directed through the chambers for 10 min or longer, with the reservoir bag removed during this period of flushing, to ensure denitrogenation. The system was then sealed except for the opening to the oxygen bypass.

Anesthetic was introduced in an amount calculated to produce a rapid increase to the desired concentration. The concentrations actually achieved were determined from gas samples obtained from the chambers in sequence, usually at 10–15-min intervals.

During anesthesia, the rectal temperature of each rat was maintained between 37.5 and 38.5°C by applying heat (infrared lamps) or cold (ice) to the outside of the chambers. Carbon dioxide concentrations were measured during each study (infrared analysis with a Beckman LB-2 analyzer) and usually were between 0.7 and 1.0%, the highest measuring 1.5%. Oxygen concentrations, also measured during each study (Beckman E2 Pauling meter, calibrated with nitrogen and oxygen each day), were never less than 75%.

At the end of the specified period of each anesthetic study, the reservoir bag was removed and oxygen flushed through the system for a few seconds before the rats were removed from their chambers and placed supine. Temperature probes were left in place, and

Table 2. Minutes to Righting

Hr	MAC	I-653	Sevoflurane	Isoflurane	Halothane
0.5	1.6	2.4 ± 1.6	4.8 ± 2.1	7.5 ± 5.7	11.5 ± 3.8
1.0	1.6	3.5 ± 2.5	5.4 ± 3.0	8.2 ± 5.1	17.0 ± 5.9
2.0	1.6	4.4 ± 2.3	6.2 ± 3.1	9.7 ± 4.5	25.0 ± 8.5
2.0	1.2	1.1 ± 0.7	5.4 ± 2.8	10.1 ± 8.0	21.3 ± 11.1
2.0	0.8	0.3 ± 0.8	4.0 ± 2.7	8.8 ± 9.0	11.6 ± 13.4
2.0	0.4	—	0.8 ± 1.8	0.9 ± 2.2	1.0 ± 1.2

Values are expressed as mean ± SD.

n = 8 for all groups except those given 1.6 MAC for 2.0 hr. For this last group, *n* = 12.

Table 3. Minutes to Pass Rotarod Test

Hr	MAC	I-653	Sevoflurane	Isoflurane	Halothane
0.5	1.6	3.4 ± 1.2	7.7 ± 1.6	11.6 ± 4.7	16.1 ± 2.7
1.0	1.6	4.8 ± 2.1	10.5 ± 2.8	14.6 ± 1.9	31.5 ± 3.6
2.0	1.6	9.8 ± 4.1	15.0 ± 4.8	35.8 ± 7.6	56.2 ± 6.9
2.0	1.2	4.7 ± 3.0	14.2 ± 8.1	23.2 ± 4.7	47.2 ± 4.7
2.0	0.8	1.4 ± 1.5	6.9 ± 2.6	14.2 ± 7.6	23.6 ± 8.6
2.0	0.4	—	2.2 ± 1.6	3.4 ± 1.2	3.8 ± 1.4

Values are expressed as mean ± SD.

n = 8 for all groups except those given 1.6 MAC for 2.0 hr. For this last group, *n* = 12.

heat was applied to the rats to help maintain their temperature; temperatures invariably decreased slightly after removal from the tubes. The time each rat required to right himself twice, righting being defined as turning to position all four feet on the table, was measured and recorded.

Immediately after the second righting, the temperature probe was removed, and each rat was tested for the ability to remain upright on the rotarod for 60 sec. The test was repeated thereafter at intervals determined by multiples of three (i.e., at 3, 6, 9, 12 min etc.) from the time anesthesia was discontinued. Each rat was given two chances to pass the rotarod test at each interval. When position atop the rotarod could be maintained for 60 consecutive sec, the study was concluded.

No rat was given more than one concentration of one anesthetic. The concentrations and durations for all anesthetics except I-653 were 0.4 MAC, 0.8 MAC, 1.2 MAC, and 1.6 MAC for 2 hr, and 1.6 MAC for 0.5 hr and 1.0 hr (Table 1). The 0.4 MAC determination was not made with I-653 because the rats awakened immediately at the 0.8 MAC level. The MAC values assumed were 5.7% I-653 (6), 1.1% halothane (7), 1.4% isoflurane (7), and 2.5% sevoflurane (8).

Data Analysis

The results for times to recovery were subjected to a determination of mean and standard deviation values. A regression analysis was applied separately to

the data obtained at constant duration of anesthesia and at constant anesthetic dose.

Results

The desired anesthetic concentrations were rapidly achieved in all cases. The average concentration obtained for I-653 in the groups of four rats was $96.9 \pm 4.4\%$ (mean ± SD; *n* = 11) of the desired concentration, and $102.8 \pm 4.7\%$ for halothane (*n* = 13), $101.2 \pm 8.4\%$ for isoflurane (*n* = 13), and $103.4 \pm 8.4\%$ for sevoflurane (*n* = 13). The anesthetic effect was apparent soon after injection of the agent into the system and was associated with a tendency toward a decrease in temperature, which was prevented by heating the chambers with infrared lamps.

At a given MAC multiple and duration, recovery from I-653 was always most rapid, followed by sevoflurane, then isoflurane, and finally halothane (Tables 2 and 3; Figs. 2-4). Results for the recovery of the righting reflex were more variable than those for recovery of motor coordination (the rotarod test) (Tables 2 and 3). Consistent with this difference in variability, regression analyses using the righting reflex produced lower correlation coefficients (Tables 4 and 5). Moreover, the data for the righting reflex tended to be skewed, the median being well below the mean in most cases. Although the skewed data could be corrected by taking the square root of the times to recovery (a logarithmic correction could not be applied because values for the 0.4 MAC concentration

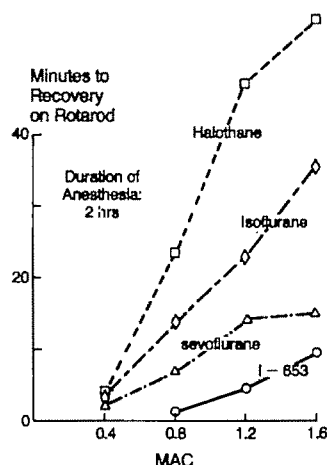


Figure 2. An increase in the delivered concentration of anesthetic (duration of anesthesia constant at 2 hr) increased the time to recovery of the motor coordination necessary to remain atop a 6-cm rod rotating at 8 rpm (rotarod recovery). The slope of the increase was proportional to the solubility of the anesthetic, steepest with the most soluble agent, halothane, and least so with the least soluble agent, I-653.

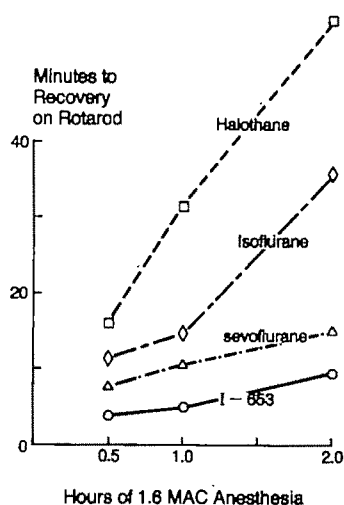


Figure 3. An increase in the duration of anesthesia (dose constant at 1.6 MAC) increased the minutes to rotarod recovery after anesthesia. As with Figure 2, the time to recovery was a function of the solubility of the anesthetic. The slope of the increase was proportional to the solubility of the anesthetic, steepest with the most soluble agent, halothane, and least so with the least soluble agent, I-653.

were sometimes zero), this tactic improved the correlation only marginally (Tables 4 and 5).

It appears that at a concentration of 0.8 MAC or greater, the product of anesthetic duration and anesthetic dose produces the same time to recovery regardless of whether the concentration produces a light or deep level of anesthesia. That is, at anesthetizing concentrations, the MAC-hours of anesthesia determine the time to recovery (Fig. 4).

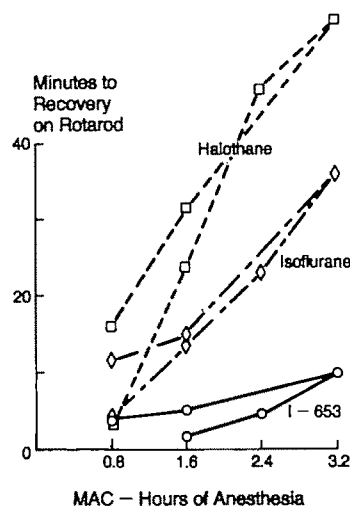


Figure 4. The data for Figures 2 and 3 are combined for I-653, isoflurane, and halothane by altering the abscissa to "MAC-Hours of Anesthesia." The data indicate a separation of the curves for a given anesthetic at shorter durations of deep anesthesia vs long duration of light anesthesia, e.g., the separation at 0.8 MAC-hours. This separation narrows at higher MAC-hours. That is, higher concentrations given for a shorter time produce the same effect on the time to recovery as longer durations of exposure at lighter levels of anesthesia.

Discussion

The times to recovery from anesthesia in rats correlated with the values for the solubility of the anesthetics in human blood (Fig. 5). It is not certain that these values for recovery may be quantitatively applied to humans. Because human blood tends to have a lower affinity for anesthetic (a lower blood/gas partition coefficient) than rodent blood (9-11), our results may give an overestimate for recovery times in humans. However, the effect of the greater solubility in rodent blood on rate of recovery appears to be more than compensated for by the greater ventilation and cardiac output (and hence shorter time constants for lung and tissue) found in small animals (9). Furthermore, we applied inspired rather than alveolar concentrations of anesthetic, and thus the rats given more soluble agents had a relatively lower MAC than indicated. Our data, therefore, may underestimate the differences to be found in humans.

However, clinical data for recovery from isoflurane and from halothane do not suggest that we have underestimated the differences. Although some studies suggest that recovery is more rapid with isoflurane (12-14), others report little or no difference in recovery from these two agents (15,16). In part, the absence of any notable difference may result from the clinical use of light levels of anesthesia and the common use of nitrous oxide as an adjuvant. In most studies, nitrous oxide produces the major portion of the anes-

Table 4. Data from Regression Analyses, Constant Duration of Anesthesia, Anesthetic Dose Varied

Variable	I-653	Sevoflurane	Isoflurane	Halothane
Righting Reflex				
Y Intercept ^a	-4.4 ± 1.2	-0.1 ± 1.1	0.8 ± 2.7	-5.3 ± 4.0
Slope ^b	5.3 ± 1.0	4.2 ± 1.0	6.4 ± 2.3	19.9 ± 3.4
r ²	52%	34%	16%	48%
r ²⁺	68%	47%	35%	63%
Rotarod Recovery				
Y Intercept ^a	-7.4 ± 2.4	-1.5 ± 2.1	-7.5 ± 2.5	-11.9 ± 2.9
Slope ^b	10.6 ± 1.8	11.0 ± 1.8	26.7 ± 2.2	44.3 ± 2.5
r ²	55%	51%	81%	90%
r ²⁺	64%	61%	85%	88%

r²⁺ is the value for slope after conversion of the times to awakening to the square root of the times to awakening.

For all correlation coefficients, $P < 0.001$ except for the correlation of 16% where $P < 0.01$.

^aMinutes.

^bIncrease in minutes to awakening/MAC increase.

Table 5. Data from Regression Analyses, 2 MAC, Anesthetic Duration Varied

Variable	I-653	Sevoflurane	Isoflurane	Halothane
Righting Reflex				
Y Intercept ^a	2.0 ± 0.9	4.4 ± 1.2	6.7 ± 2.1	7.6 ± 2.8
Slope ^b	1.2 ± 0.6	0.9 ± 0.8	1.5 ± 1.4	8.8 ± 1.9
r ²	10%	0%	0%	42%
r ²⁺	12%	1%	3%	43%
Rotarod Recovery				
Y Intercept ^a	0.9 ± 1.2	4.9 ± 1.5	0.9 ± 2.5	3.8 ± 2.2
Slope ^b	4.4 ± 0.9	5.1 ± 1.0	17.1 ± 1.8	26.4 ± 1.5
r ²	48%	46%	77%	92%
r ²⁺	57%	51%	81%	92%

r²⁺ is the value for slope after conversion of the times to awakening to the square root of the times to awakening.

For all correlation coefficients >40% $P < 0.001$; for $r^2 = 10$ –12%, $P < 0.05$; values for r^2 or r^{2+} below 10% were not significant.

^aMinutes.

^bIncrease in minutes to awakening/hour of anesthesia.

thetic effect. As suggested by Figure 5, the difference in recovery time among agents of different solubilities is small after administration of light levels of anesthesia. That is, the slope decreases as the MAC applied decreases.

Another reason for differences in the time to recovery among humans may be a consequence of the selection of different end points. The measurement of time to recovery of consciousness (perhaps akin to the time to recovery of the righting reflex) may not be as sensitive or important a measure as the time to recovery of some element of adequate coordination (akin to the time to recovery of the ability to maintain position on the rotarod).

As common sense and clinical observation would predict, our results demonstrate that both anesthetic dose (Fig. 2) and anesthetic duration (Fig. 3) correlate with the time to recovery from anesthesia. However, the correlation differs among anesthetics as a function of solubility, and the strongest correlations (steepest

slopes) are associated with anesthetics of greatest solubilities (Tables 4 and 5). The difference among anesthetics becomes small at low anesthetic concentrations or short-term anesthesia.

Although our data do not demonstrate it, we predict that prolonged anesthesia should not produce proportional increases in the time to recovery. Ultimately, the body stores of anesthetic should be filled, and longer durations of anesthesia should not increase the amount of anesthetic stored. If the body stores of anesthetic are not increased, then the time to awakening should not be increased unless the time to awakening is a function of some time-dependent central effect of anesthetic exposure rather than a function of the blood anesthetic concentration. This possibility seems unlikely; if it were true recovery from a prolonged anesthesia with a poorly soluble drug might take as long as recovery from a highly soluble agent. This prediction is not consistent with our findings.

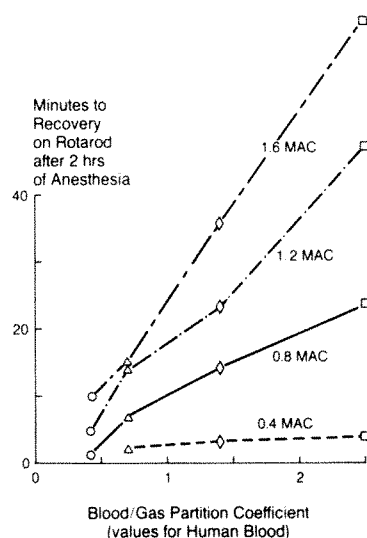


Figure 5. The time to recovery from anesthesia appears to be a rectilinear function of solubility at all levels of exposure to a given concentration of anesthetic. The slope relating time to recovery and anesthetic solubility increases with an increase in the concentration of anesthetic. The points at a blood/gas partition coefficient of 0.42 (○) are for I-653, at 0.69 (△) are for sevoflurane, at 1.4 (◇) are for isoflurane, and at 2.5 (□) are for halothane.

Recovery was most rapid after anesthesia with I-653 regardless of the duration of anesthesia and the inspired anesthetic concentration. This outcome indicates a particular advantage to the use of I-653 in anesthesia for outpatient surgery where swift recovery of coordination should enhance the safety of ambulatory patients. A more rapid recovery should decrease the danger of patient injury from falling and reduce the time to the safe operation of equipment requiring manual dexterity such as driving a car. Our results also suggest that the administration of levels of I-653 deep enough to produce hypotension or muscle relaxation should not unduly prolong recovery from anesthesia.

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Stability of I-653 in Soda Lime

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EGER EI II. Stability of I-653 in soda lime. *Anesth Analg* 1987;66:983-5.

Stability is an important characteristic of a halogenated volatile anesthetic because breakdown may produce toxic compounds. The resistance to breakdown by soda lime of a new halogenated volatile anesthetic, I-653, was compared with the resistances found for halothane, isoflurane, and sevoflurane. The four anesthetics were injected concurrently into flasks containing 500 ml of gas and 100 g of soda lime maintained at 40, 60, and 80°C. Four or five flasks were tested at each temperature. The rate of anesthetic degradation

increased as temperature increased. Degradation was greatest with sevoflurane and least with I-653. At 80°C, the rate of degradation per hr was $92.2 \pm 5\%$ with sevoflurane; $16.0 \pm 1.6\%$ with halothane; $13.1 \pm 3.7\%$ with isoflurane; and $0.44 \pm 0.26\%$ with I-653 (means $\pm$ SD). The in vitro stability of I-653 suggests that it may strongly resist biodegradation.

Key Words: ANESTHETICS, VOLATILE—I-653, halothane, isoflurane, sevoflurane. CARBON DIOXIDE, ABSORPTION—soda lime.

I-653 is a new, volatile anesthetic that differs from isoflurane by substitution of a fluorine atom for the chlorine found on the α -ethyl component of isoflurane. Thus its formula is $\text{CF}_2\text{H}-\text{O}-\text{CFH}-\text{CF}_3$. The substitution of fluorine for chlorine markedly decreases the blood solubility of I-653 from that of isoflurane (blood gas partition coefficients 0.42 vs 1.41, respectively) (1,2), and should also increase stability. A greater stability is desirable; an unstable anesthetic may degrade to toxic compounds in vitro (3-6) and in vivo (7). The following experiment compared the stability of I-653 with the stability of halothane, isoflurane, and sevoflurane in the presence of soda lime at 40, 60, and 80°C.

Methods

Three groups of four and one group (80°C) of five 581-ml flasks were filled with 100 g of fresh soda lime (Sodasorb) containing approximately 15% water by weight. The surface of the soda lime was covered with a Teflon cup to prevent liquid (but not gaseous) anesthetic from reaching the soda lime. Teflon stoppers pierced with needles capped with one-way stopcocks

were used to seal the flasks. After air was evacuated from each flask, a liquid mixture of the four anesthetics was added to each. The total liquid volume injected was calculated to produce an initial vapor concentration of 1-3% of each agent. Such concentrations were more than an order of magnitude less than the saturated vapor pressure (i.e., all anesthetic was vaporized). The vapor pressure of I-653 is slightly greater than 700 mm Hg at 23°C (unpublished data). Such vapor concentrations are approximately those used in clinical practice: MAC for sevoflurane in humans is 1.71% (8); that for halothane is 0.75% (9); and that for isoflurane is 1.4% (10). MAC for I-653 in rats is 5.7% (11). Each flask was placed in a waterbath and after 20-30 min, the pressure in each was allowed to reach ambient pressure by the admission of room air. The concentration of each anesthetic was determined by gas chromatography.

For chromatography we used a 30-m, fused silica open tubular capillary column (0.53 mm internal diameter) coated with a layer of methylsilicone oil 1.5- μm thick (J & W Scientific DB-1). A nitrogen carrier stream of 6 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop.

The first group of four flasks was maintained at 40°C, the second group of four at 60°C, and the last two groups (four and five flasks respectively) at 80°C. The gas in the flasks was serially sampled (sample

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Table 1. Rate of Anesthetic Degradation in Soda Lime (%/hr)

Temperature	I-653	Halothane	Isoflurane	Sevoflurane
40°C	0.083 ± 0.086	0.63 ± 0.11	0.20 ± 0.09	12.9 ± 0.4
60°C	-0.094 ± 0.071	1.56 ± 0.07	0.15 ± 0.06	56.4 ± 4.3
80°C	0.45 ± 0.26	16.0 ± 1.6	13.1 ± 3.7	92.2 ± 5.2

The rates of degradation reported (mean ± SD) are for the indicated agent placed in a 581-ml flask containing 100 g soda lime. All values for the above rates of degradation differ significantly from zero except for those for I-653 at 40 and 60°C. All values for a given agent differ from the values for the remaining agents at a given temperature. The values for each anesthetic at each temperature are the average from four determinations except for I-653, isoflurane, and halothane at 80°C, where the average for each agent is from five determinations.

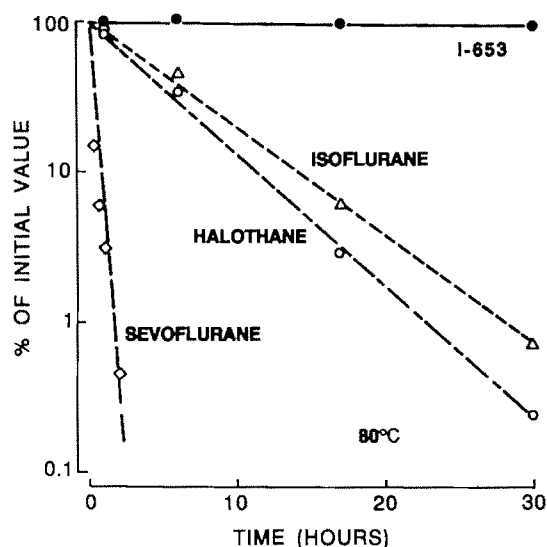


Figure 1. Individual data are presented for the four agents studied at 80°C. Four or five such slopes were obtained for each agent at each temperature.

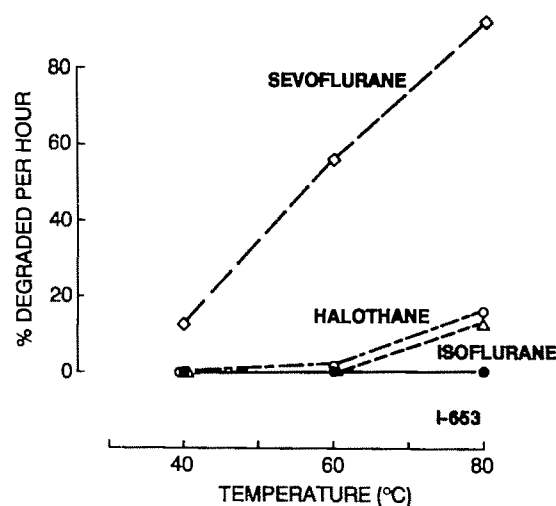


Figure 2. Except for the absence of a change for I-653 between 40 and 60°C, the rates of degradation of all anesthetics increased as temperature increased from 40 to 80°C. Stability was best preserved with I-653.

size 8 ml) over the next several hours or days (five to nine samples per flask). Two sets of flasks were studied at 80°C because sevoflurane degraded so rapidly that it required sampling at short intervals to accurately calculate the rate of breakdown. The remaining agents decayed at a much slower rate.

The concentrations of each anesthetic at each temperature were plotted against time for the four groups of flasks, and a regression analysis was applied to the data for individual anesthetics for each flask at each temperature, assuming a logarithmic decay. Average slope and standard deviation were determined for the four or five values obtained at each temperature for all four anesthetics. A *t*-test was used to determine whether a significant deviation from zero (no anesthetic decay) arose for the average of the slopes of each regression equations for each anesthetic at each temperature. A paired *t*-test (with a Bonferroni correction for multiple comparisons) was used to determine whether the slopes for the anesthetics differed

from each other. For all calculations, differences were considered significant when $P < 0.01$.

Results

Although I-653 did not degrade significantly at 40 or 60°C, it did so at 80°C (Table 1). All the remaining agents degraded at all temperatures (that is, the slope for concentration of anesthetic vs time deviated from zero) (Table 1, Fig. 1). With the exception of the 40–60°C comparison for I-653, for all anesthetics, the rate of degradation increased with each increase in temperature (Table 1, Fig. 2). At all temperatures, the rate of degradation was lowest with I-653 and highest with sevoflurane (Table 1, Figs. 1 and 2). Isoflurane and halothane occupied intermediate positions, with halothane degradation occurring at a faster rate. In all but three comparisons of the average degradation values for each anesthetic, the differences among anesthetics were highly significant ($P < 0.001$). The differences

among the three exceptions were less dramatic, but still significant ($P < 0.01$).

Discussion

The results indicate that I-653 is considerably more stable in soda lime than any of the presently used potent volatile anesthetics. At 80°C the stability of I-653 was 29-fold greater than that of isoflurane, the next most stable agent. Such high stability is a desirable property because both in vitro and in vivo breakdown products may be toxic.

The results obtained for halothane, isoflurane, and sevoflurane in the present study are relatively consistent with those previously reported (12). The methods applied in the earlier study were similar to those used in the current experiment except for three conditions: in the previous investigation somewhat lower temperatures were applied; water was added to the soda lime; and regression analyses were performed on grouped data. Despite these differences, the results of both studies are qualitatively similar. There is a small quantitative difference in that the results for the current experiment indicate slightly slower rates of degradation than reported earlier. For example, in the previous study, at 54°C, the rates of degradation for halothane, sevoflurane, and isoflurane were 2.21%/hr, 57.4%/hr, and 0.30%/hr, respectively. In the present study, at 60°C, these rates were 1.56%/hr, 56.4%/hr, and 0.15%/hr, respectively.

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Lack of Influence of Cimetidine on Bupivacaine Levels during Parturition

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The concurrent use of cimetidine as a prophylactic antacid and bupivacaine as a local anesthetic for epidural anesthesia for cesarean section has been promoted. However, cimetidine is known to inhibit clearance of many drugs by reducing hepatic blood flow and by inhibiting cytochrome P-450 enzymes. The purpose of this study was to determine whether cimetidine during epidural anesthesia alters the metabolism, disposition, protein binding, or placental transfer of bupivacaine. Thirty-six patients undergoing cesarean section with 0.5% bupivacaine for epidural anesthesia were studied. Sixteen patients received cimetidine (300 mg IM) 1-4 hr before cesarean section and 20 control patients received sodium citrate (30 ml PO) 10 min preoperatively. Bupivacaine and

its inactive metabolite, 2,6-pipecolylxylidine (PPX) were quantitated by gas chromatography/mass spectrometry. Maternal plasma concentration time curves, fetal/maternal ratios at delivery, cord vein/cord artery ratios, PPX/bupivacaine ratios, and maternal and neonatal urinary excretion were compared between the two groups. No significant differences could be found between the groups in any of the outcome variables. However, in the presence of cimetidine, the percentage of unbound bupivacaine significantly increased from 1.36 ± 0.53 to $1.66 \pm 0.78\%$. The results suggest that a single 300-mg IM dose of cimetidine does not significantly affect bupivacaine disposition or metabolism in parturients when given 1-4 hr before anesthesia.

Key Words: ANESTHETICS, LOCAL—bupivacaine. GASTROINTESTINAL TRACT, STOMACH—cimetidine. BICTRANSFORMATION—bupivacaine.

There are numerous reports (1-5) of increased toxicity of drugs with concurrent administration of cimetidine. Cimetidine has been reported to decrease liver blood flow (6), inhibit metabolism of drugs by the cytochrome P450 enzyme system (7), and decrease protein binding of certain drugs (8). Thus, the elimination of drugs that are highly dependent on hepatic blood flow, which undergo oxidative metabolism, and which are highly protein-bound, have the potential for increased toxicity in the presence of cimetidine. For example, it is well known that cimetidine decreases hepatic clearance and protein binding of lid-

ocaine, an amide local anesthetic (8-10). Although most reports of decreased liver blood flow or interactions involve chronic administration of cimetidine, effects after single doses have also been reported (3-6).

Bupivacaine, an amide local anesthetic similar in structure to lidocaine, is highly protein-bound, undergoes oxidative metabolism, and has a narrow therapeutic range because of its cardiotoxicity (11). It is commonly used in obstetrics for epidural anesthesia. Any interaction between cimetidine and bupivacaine is of interest because cimetidine is likely to be used for aspiration pneumonitis prophylaxis before cesarean section performed under epidural anesthesia with bupivacaine.

Previous work with animals (12) has shown that cimetidine inhibits in vitro bupivacaine metabolism by microsomes and hepatocytes, decreases protein binding of bupivacaine, and increases the plasma half-life after a single dose. Therefore, the purpose of this study was to determine whether a single dose of cimetidine before epidural anesthesia alters the metabolism, disposition, protein binding, or placental transfer of bupivacaine.

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Table 1. Maternal Characteristics

Maternal characteristics	Control (n = 20)	Cimetidine-treated (n = 16)
Age (yr)	29 ± 5 ^a	25 ± 4
Parity		
Nulliparous	1	1
Multiparous	19	15
Delivery method		
Repeat cesarean	17	15
Primary cesarean	3	1
Intrapartum anesthesia		
Total mg 0.5% bupivacaine	132 ± 33	128 ± 30
Anesthesia to delivery interval (min)	45 ± 12	48 ± 12
Complications		
>200 lbs	4	2
Class 1 heart disease	1	1
Gestational diabetes	1	2
Chronic hypertension	1	0

^a $\bar{X} \pm SD$.

Table 2. Characteristics of the Neonates

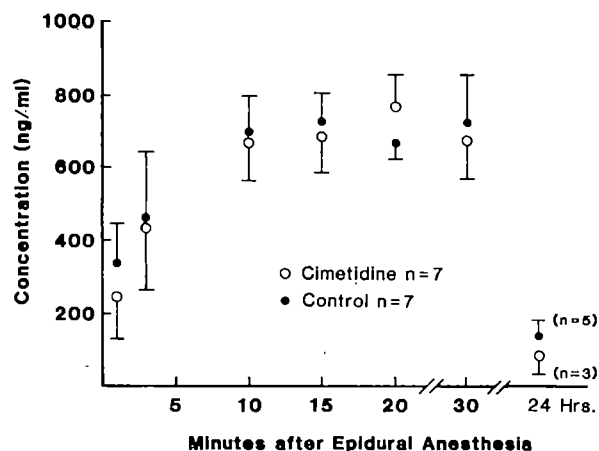
Neonatal characteristics	Control (n = 20)	Cimetidine-treated (n = 16)
Gestational age (weeks)	40 ± 1.4 ^a	40 ± 1.2
Birthweight	3309 ± 584	3313 ± 398
Apgar score <7		
1 min	3	1
5 min	0	0
Cord venous pH	7.31 ± 0.06	7.34 ± 0.03
Cord artery pH	7.24 ± 0.07	7.26 ± 0.06
Complications		
Large for dates	3	3
Sepsis	0	1
Micrognathia	1	0

^a $\bar{X} \pm SD$.

Materials and Methods

Thirty-six pregnant women and their infants were studied during and after delivery by cesarean section under epidural anesthesia with 0.5% bupivacaine without epinephrine. To qualify, the patients had to be classified as ASA categories 1 or 2, be a candidate for epidural anesthesia, and be at term. The clinical characteristics of the mothers and neonates, the amount of bupivacaine used, and the timing of anesthesia are shown in Tables 1 and 2. Preoperatively, 16 study patients received cimetidine (300 mg IM) 1–4 hr (150 ± 54 min, range 80–258) before cesarean section, and 20 control patients received sodium citrate (30 ml) 10 min preoperatively. The study was approved by the Human Investigation Committee of Cleveland Metropolitan General Hospital and informed consent was obtained from each patient.

Maternal peripheral venous blood samples (3 ml) were collected as reported previously (13). Maternal

Figure 1. Maternal plasma levels of bupivacaine after epidural anesthesia for cesarean section ($\bar{X} \pm SEM$).Table 3. Bupivacaine Levels at Delivery in Control and Cimetidine-Treated Parturients ($\bar{X} \pm SD$)

Bupivacaine (ng/ml)	Control (n = 20)	Cimetidine-treated (n = 16)	Significance level
Maternal vein	901 ± 290	908 ± 290	NS ^c
Cord vein	271 ± 104	236 ± 110	NS
Cord artery	176 ± 110 ^a	141 ± 78 ^b	NS

^an = 18.^bn = 12.^cNot significant.Table 4. PPX Levels at Delivery in Control and Cimetidine-Treated Parturients ($\bar{X} \pm SD$)

PPX (ng/ml)	Control (n = 20)	Cimetidine-treated (n = 16)	Significance level
Maternal vein	34 ± 2	36 ± 3	NS ^a
Cord vein	21 ± 11	23 ± 12	NS

^aNot significant.

and neonatal samples were also obtained 24, 48, and 72 hr after delivery. Six consecutive 6-hr samples of maternal and neonatal urine were collected after delivery. Not all samples could be collected from all patients.

Levels of bupivacaine and its pharmacologically inactive metabolite, 2,6-pipecolylxylidine (PPX) produced by dealkylation, were determined in plasma and urine using gas chromatography/mass spectrometry (13).

Semilogarithmic plots were made of levels of bupivacaine and PPX in maternal plasma, fetal/maternal plasma concentration ratios, the ratio between cord arterial and cord venous bupivacaine concentration, the ratio of PPX/bupivacaine at delivery, and PPX/total product ratios; and linear plots were made showing urinary levels of bupivacaine and PPX in the neonate

Table 5. Cord Vein/Maternal Vein and Cord Artery/Cord Vein Ratios in Control and Cimetidine-Treated Parturients ($\bar{X} \pm \text{SD}$)

	Control (<i>n</i> = 20)	Cimetidine-treated (<i>n</i> = 16)	Significance level
Bupivacaine			
Cord vein/maternal vein	0.32 $\pm$ 0.16	0.27 $\pm$ 0.11	NS ^d
Cord artery/cord vein	0.67 $\pm$ 0.24 ^a	0.66 $\pm$ 0.31 ^b	NS
PPX			
Cord vein/maternal vein ^c	1.01 $\pm$ 1.00	0.83 $\pm$ 0.71	NS

^a*n* = 17.^b*n* = 11.^cMean of ratios (not ratio of means).^dNot significant.**Table 6.** PPX Levels at Delivery in Control and Cimetidine-Treated Parturients ($\bar{X} \pm \text{SD}$)

PPX (ng/ml)	Control (<i>n</i> = 20)	Cimetidine-treated (<i>n</i> = 16)	Significance level
Maternal vein	34 $\pm$ 2	36 $\pm$ 3	NS ^a
Cord vein	21 $\pm$ 11	23 $\pm$ 12	NS

^aNot significant.

as a function of time. Urinary levels of drug or metabolite data were expressed as $\mu\text{g/ml}$ urine. The total amounts of PPX and bupivacaine excreted by the mother were also determined.

Maternal plasma was obtained from seven parturients before administration of analgesia or anesthesia for delivery. These patients were without medical complications and delivered at term. Bupivacaine binding to protein in these samples was determined by equilibrium dialysis against a 0.08 mol/L Na_2HPO_4 0.03 mol/L NaH_2PO_4 buffer (1 ml; pH 7.4) for 4 hr at 37°C. The experiments were done at two initial concentrations of cimetidine in the chamber (1 or 2 $\mu\text{g/ml}$) at a concentration of 1 $\mu\text{g/ml}$ bupivacaine.

Student's *t*-tests and analysis of variance (ANOVA) were used to compare levels of bupivacaine, ratios, and amount excreted by the two groups. Power analysis showed that 10–15 patients would be required per group to show whether statistically significant differences did or did not exist in the various parameters of interest (14). One-tailed paired *t*-tests were used to analyze data from the protein binding experiments. Statistical significance was accepted at $P < 0.05$.

Results

Patient characteristics are shown in Tables 1 and 2. All of the women underwent scheduled cesarean sections at term. The primary cesarean sections were performed because of previous uterine surgery or abnormal presentations.

Table 7. Bupivacaine Levels (ng/ml) in Neonatal Plasma at Various Times after Delivery ($\bar{X} \pm \text{SD}$) and Half-Life Calculated from Mean Plasma Data

	Control (<i>n</i> = 15)	Cimetidine-treated (<i>n</i> = 13)
Delivery (cord vein)	261 $\pm$ 112	214 $\pm$ 105
24 hr	9 $\pm$ 9	13 $\pm$ 14
48 hr	1.8 $\pm$ 4	5 $\pm$ 5
72 hr	0.8 $\pm$ 3	0.5 $\pm$ 1
Half-life (hr)	8.77	8.66

There were no statistically significant differences between the groups in bupivacaine levels in maternal plasma (Fig. 1), in bupivacaine and PPX levels at delivery (Tables 3 and 4), in cord vein/maternal vein or cord artery/cord vein ratios (Table 5), in PPX/bupivacaine ratios at delivery (Table 6), in rate of disappearance of bupivacaine from neonatal plasma (Table 7), or in rate of disappearance of bupivacaine from maternal (Table 8) or neonatal urine (Fig. 2 and 3).

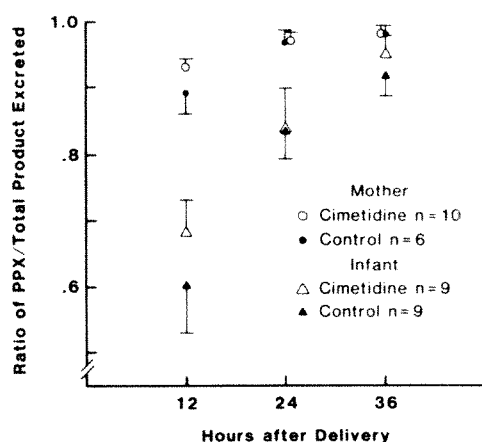
There were significant differences in protein binding after exposure to cimetidine. An average of $1.36 \pm 0.63\%$ of the bupivacaine was unbound by maternal plasma proteins before incubation with 1 or 2 μg of cimetidine. After exposure to cimetidine, $1.66 \pm 0.78\%$ of the bupivacaine was free in the plasma; this represented a 22% increase in free bupivacaine in maternal plasma and was statistically significant. There was no change in protein binding when the cimetidine concentration increased from 1 to 2 $\mu\text{g/ml}$.

Discussion

We are not aware of any previous studies on the interaction between cimetidine and bupivacaine in humans. Therefore, the purpose of this study was to determine whether a single dose of cimetidine alters the metabolism, disposition, protein binding, or placental transfer of epidural bupivacaine during par-

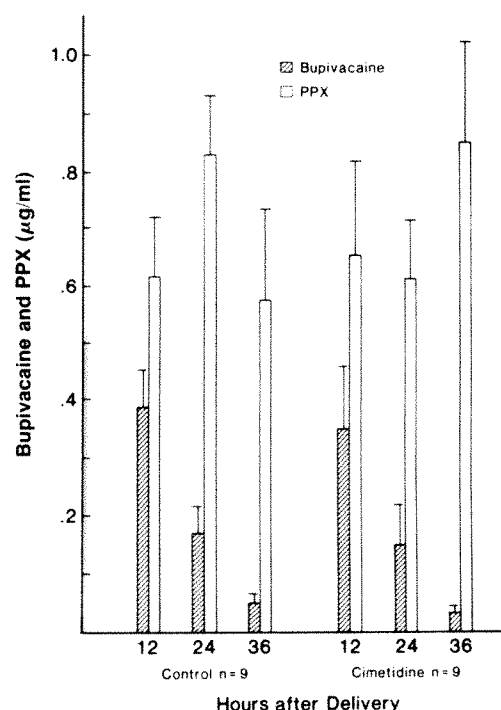
Table 8. Bupivacaine and PPX Excretion by Control and Cimetidine-Treated Parturients ($\bar{X} \pm \text{SD}$)

	Control (n = 6)	Cimetidine-treated (n = 10)	Significance level
Total bupivacaine excreted (μg)	597 $\pm$ 381	594 $\pm$ 373	NS ^a
PPX	11,860 $\pm$ 5210	13,732 $\pm$ 7382	NS
Percent of metabolite to total product excreted	95 $\pm$ 3	95 $\pm$ 2	NS
Percent of total dose excreted	11 $\pm$ 5	11 $\pm$ 6	NS

^aNot significant.Figure 2. Ratio of PPX, a metabolic product of bupivacaine, to total products (PPX plus unchanged bupivacaine) excreted by cimetidine-treated and control patients ($\bar{X} \pm \text{SEM}$).

turition. The data suggest that any slight inhibition in metabolism of bupivacaine that may occur due to a single dose of cimetidine 1-4 hr before delivery is offset by small increases in the fraction of unbound bupivacaine. The net result is that there is no alteration in bupivacaine disposition after a single dose of cimetidine. Pharmacologic data from both the control and the study group agree well with previously published data obtained using the same analytic technique (13).

Bupivacaine is highly protein-bound and, in monkeys, this binding is decreased from 93.59 to 91.06% at concentrations of 1 $\mu\text{g}/\text{ml}$ cimetidine (12). In monkeys, the increase in plasma levels of free bupivacaine caused by cimetidine offsets any reduction in hepatic clearance due to enzyme inhibition that is caused by cimetidine, and thus total clearance of bupivacaine does not change (12). In the present study, the reduction in protein binding was statistically, although probably not clinically, significant (98.64 to 98.35%). Thus, the findings of the present study are consistent with the pharmacologic characteristics of bupivacaine and are supported by previous findings in monkeys. The results of this study indicate that single doses of cimetidine used clinically for aspiration pneumonitis

Figure 3. Excretion of bupivacaine and PPX by infants of mothers given cimetidine and by control infants ($\bar{X} \pm \text{SEM}$).

prophylaxis do not significantly increase bupivacaine toxicity during epidural anesthesia for cesarean section.

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Bunegin-Albin Catheter Improves Air Retrieval and Resuscitation from Lethal Venous Air Embolism in Dogs

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COLLEY PS, ARTRU AA. Bunegin-Albin catheter improves air retrieval and resuscitation from lethal venous air embolism in dogs. *Anesth Analg* 1987;66:991-4.

Three types of catheters, the single-orifice Sorenson CVP kit catheter, the right atrial (RA) port of an American Edwards 7F Swan-Ganz catheter, and the Cook Bunegin-Albin multi-orifice CVP catheter were evaluated for their ability to retrieve venous air emboli and effect on the success rate of resuscitation from venous air emboli. The catheters were inserted in anesthetized dogs in the prone position. Swan-Ganz catheters were positioned with the RA port just above the junction of the superior vena cava (SVC) and the RA, single-orifice Sorenson catheters with the orifice tip located either just above the SVC-RA junction or in the mid-RA, and Bunegin-Albin multiorifice catheters with the proximal orifice just above the SVC-RA junction and the distal orifice near the mid-RA. Dogs were then given a predetermined

lethal dose of air (5 ml/kg) over 30 sec via the femoral vein. Attempts to aspirate venous air emboli were begun with first decrease in expired CO₂. The amounts of air retrieved and the incidence of successful resuscitation were compared. Significantly greater percentages of injected venous air were retrieved with the Bunegin-Albin catheter (60 ± 7%) than with the Sorenson catheter in the SVC (16 ± 6%), with the Sorenson catheter in the mid-RA (10 ± 3%) or with the Swan-Ganz RA port (4 ± 1%). Resuscitation was significantly more often successful with the Bunegin-Albin catheter (six of nine dogs) than with either Sorenson catheter (zero of seven in both groups) or the Swan-Ganz RA port (one of seven). The Cook Bunegin-Albin multi-orifice catheter appears to be superior to the Sorenson or Swan-Ganz RA port for aspiration of air after venous air embolism.

Key Words: EMBOLISM—AIR.

Controversy exists over which, if any, venous catheter should be inserted into patients at risk for venous air embolism. Some advocate placement of two-lumen Swan-Ganz pulmonary artery catheters, whereas others prefer placement of single-lumen right atrial (RA) catheters (1). Swan-Ganz catheters can detect very early the increase in pulmonary artery pressure that occurs with venous air emboli and can also detect left-to-right atrial pressure gradients that can in turn lead to systemic air embolism if the foramen ovale is patent (2,3). However, the Swan-Ganz catheter has a small single lumen leading to its RA orifice that may make aspiration of air difficult from the right atrium.

In addition, there is uncertainty about the clinical efficacy of single-orifice compared with multi-orifice catheters in aspirating venous air. Bunegin et al. (4)

retrieved significantly more air with multi-orifice catheters than with single-orifice catheters in an in vitro Silastic casting of a human atrium. There are no in vivo studies, however, that corroborate these laboratory findings.

The present study was designed to determine the ability of three different catheters to retrieve venous air emboli in dogs. We used either Swan-Ganz (RA port), single-orifice, or multi-orifice long-line catheters. After determining the dose of venous air that is lethal to dogs, catheters were evaluated for percentage of injected venous air retrieved and success rate of resuscitation when air aspiration was the only method of treatment.

Methods

Dogs (weight range 14–22 kg) were anesthetized with isoflurane (> 1.7%, inspired) and N₂O (66%) in O₂. The study was approved by the Institutional Review Board. The dogs were ventilated to maintain PaO₂ > 120 mm Hg and PaCO₂ at 35–40 mm Hg. Expired CO₂ was continuously monitored using a Beckman LB-2 medical gas analyzer. An electronic offset was used to minimize interference by expired N₂O on the strip

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chart recorder display. A femoral vein was cannulated for fluid administration and for injection of air. A femoral artery was cannulated for sampling of blood for gas analysis and for continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. Temperature was monitored by a nasopharyngeal thermister probe and maintained at $37.0 \pm 0.5^\circ\text{C}$ by heat lamps or ice packs. Vascular volume was stabilized by continuous infusion of saline $4-6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. At the conclusion of the surgical preparation, wound edges were infiltrated with bupivacaine (0.75%) and the concentration of isoflurane was decreased to 0.5% (inspired, percent N_2O unchanged). The dogs were placed in the prone position and the head was slightly elevated. Once systemic variables had stabilized (> 25 min after decreasing isoflurane to 0.5%), baseline values for systemic variables were recorded. These included central venous pressure (CVP) or RA pressure, MAP, heart rate, arterial blood gas tensions, arterial blood hemoglobin levels, and nasopharyngeal temperature.

Three catheters were studied: a single-orifice Sorenson CVP Kit catheter, an American Edwards 7F Swan-Ganz catheter (RA port), and a Cook Bunegin-Albin multi-orifice CVP catheter. The Bunegin-Albin catheter has six side orifices with the most proximal orifice placed 5 cm from the catheter tip. Each catheter was examined in the position previously reported by Bunegin et al. (4) as optimum for aspirating air (Fig. 1); with the orifice near the junction of the SVC and RA for the single orifice Sorenson and Swan-Ganz catheters, and with the proximal orifice near the SVC-RA junction and distal orifice near the mid-RA for the Bunegin-Albin multi-orifice catheter. In addition, the single-orifice Sorenson catheter also was evaluated with the orifice located in the mid-RA (near the entrance of the inferior vena cava [IVC] to the RA) in view of the possibility that air entering the RA via the IVC might be preferentially retrievable from that site rather than from near the SVC-RA junction. The multi-orifice catheter was not examined at a second location because in the position recommended by Bunegin et al. (4) the distal tip was located near the mid-RA. Catheters were positioned by using the catheter as an exploring ECG lead (5).

Three anesthetized dogs were studied to determine the manner in which the ECG changes produced by the single orifice and multi-orifice catheters indicated their proximity to the SVC-RA junction. In one dog, a single-lumen, single-orifice catheter was advanced until a maximal negative P-wave deflection (without positive component) was seen. A postmortem thoracotomy was then carried out. We found that the

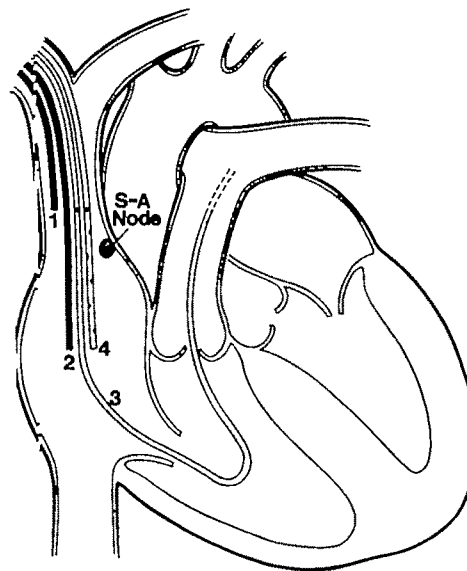


Figure 1. Location of catheters. The numbers 1 and 2 indicate Sorenson catheters; 3 is the Swan-Ganz catheter; 4 is the Bunegin-Albin catheter.

single-orifice catheter tip was at the level of the SVC-RA junction, confirming the observation of Cucchiara et al. (6). In a second dog, the Bunegin-Albin multi-orifice catheter was also advanced until a maximal negative P-wave deflection (without positive component) was seen. On postmortem thoracotomy, we found that the midpoint between tip and proximal orifice was opposite the SVC-RA junction. To eliminate the possibility that the catheter location had changed in relation to the SVC-RA junction during the process of thoracotomy and cardiac arrest, in a third anesthetized dog a Sorenson catheter and a Bunegin-Albin catheter were tied together so that their tips were level with each other. The two catheters were then inserted until a maximal negative P-wave was seen using the Sorenson catheter as an exploring ECG lead. The two catheters were then advanced until a maximal negative P-wave was seen using the Bunegin-Albin catheter as the exploring ECG lead. We found that the additional distance required to advance the Bunegin-Albin catheter to get the same wave complex as seen with the Sorenson catheter was 2.5 cm. Thus the observations in both the second and third dogs indicated that the P-wave complex originated from a point half-way between the proximal orifice and distal tip of the Bunegin-Albin catheter.

Forty-eight dogs were assigned to one of seven groups for intravenous infusion of air. Groups I ($n = 5$) and II ($n = 6$) were used to determine the lethal dose of venous air. These two groups did not have catheters placed. In the remaining five groups of dogs,

Table 1. Catheter Resistances

Catheter	Resistance (cm H ₂ O•ml ⁻¹ •min ⁻¹)
Bunegin-Albin	0.77
Swan-Ganz RA port	8.70
Sorenson	1.90

catheters were placed. The dogs in these groups were given a dose of venous air determined as being lethal in groups I and II. In group III ($n = 7$), a single-orifice catheter was placed but was not used to retrieve air. This group served as the control group for groups IV–VII. The catheter used in groups IV ($n = 7$) and V ($n = 7$) was the Sorenson catheter (lumen cross sectional area 1.4 mm²). The catheter used in group VI ($n = 7$) was the RA port of the Swan-Ganz catheter (lumen area of 0.2 mm²). The catheter used for group VII ($n = 9$) was the Bunegin-Albin multi-orifice catheter (lumen area 1.8 mm²). The resistance of these catheters are shown in Table 1.

The Sorenson catheter in group IV and RA port of the Swan-Ganz catheter in group VI were advanced until the point of maximal negative P-wave deflection with no positive P-wave component. This point was taken to indicate that the tip or port were at the SVC-RA junction. The Sorenson catheter and the RA port of the Swan-Ganz catheter were then withdrawn approximately 1–2 cm above this point. The Bunegin-Albin catheter (group VII) was advanced 1–2 cm once the point of maximum P-wave deflection was reached. Because the proximal orifice and tip are about 5 cm apart, this maneuver placed the proximal port 0.5–1.5 cm above the SVC-RA junction and the distal port in the mid-RA. The Sorenson catheter tip in group V was placed in the mid-RA as indicated by a large, equally biphasic P-wave.

Group I dogs were given 3 ml/kg air over 20 sec. Dogs in groups II–VII were given 5 ml/kg air over 30 sec. Resuscitation was attempted in groups IV–VII. The only method of resuscitation used was to aspirate venous air emboli. Attempts to aspirate air were made using a 50-ml syringe attached to the catheter. Aspiration was begun as soon as expired CO₂ decreased after injection of air. The “plunger” of the 50-ml syringe was pulled back manually with as much force as could be generated by hand. The negative force generated during aspiration was not measured. Aspiration was continued until air no longer was seen to be entering the syringe. In cases in which large amounts of air were retrieved, it was often necessary to use more than one 50-ml syringe. Invariably, blood was aspirated along with venous air emboli. Because the amount of blood was small (5–20 ml) and was not

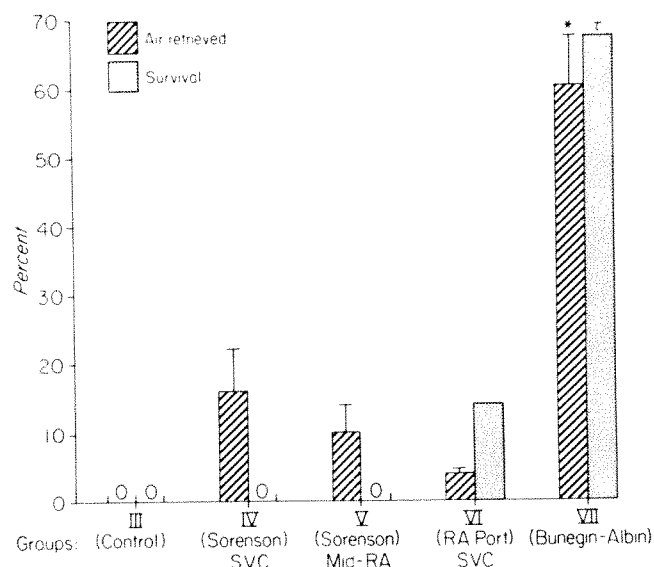


Figure 2. Results of air embolism and aspiration. Values shown are means $\pm$ SEM. The percentage of air retrieved was significantly greater (* $P < 0.05$) with the Bunegin-Albin catheter than with the RA port of the Swan-Ganz catheter or the Sorenson catheter (positioned in either the SVC or mid-RA). Also, the proportion of dogs that survived 5 ml/kg air was significantly greater ($\dagger$, $P < 0.05$) when the Bunegin-Albin catheter was used.

significantly different between groups, no attempt was made to reinfuse the aspirated blood.

The percentages of air retrieved were compared in groups IV, V, VI, and VII using Student's *t*-test for unpaired samples. The incidence of successful resuscitation was compared in groups III–VII using the variance ratio test (7). A *P* value < 0.05 was considered statistically significant.

Results

There were no differences between groups I–VII with respect to CVP or RA pressure, MAP, heart rate, temperature, PaO₂, PaCO₂, or arterial blood pH, bicarbonate and hemoglobin (not tabulated) before infusion of air.

In group I, four of five dogs survived infusion of 3 ml/kg air. In group II, however, none of the six dogs survived infusion of 5 ml/kg of air. Therefore, we determined that the lethal dose of air under our experimental conditions was 5 ml/kg of air. This dose of air was given to the dogs in group III (untreated group) and to the treatment groups IV–VII.

A significantly greater percentage of the 5 ml/kg air embolism dose was retrieved using the Bunegin-Albin catheter (60 $\pm$ 7%) (mean $\pm$ SEM) (group VII) than with either the Swan-Ganz RA port (4 $\pm$ 1%) (group VI), the Sorenson catheter in the SVC (16 $\pm$

6%) (group IV), or the Sorenson catheter in the mid-RA ($10 \pm 3\%$) (group V) (Fig. 2). The incidence of successful resuscitation from venous air embolism also was significantly higher using the Bunegin-Albin catheter (six of nine dogs) than with either of the Sorenson catheter groups (none of seven in both groups) or the Swan-Ganz RA port (one of seven).

Discussion

The origin of ECG tracing when the Bunegin-Albin multi-orifice catheter was used was midway between catheter tip and proximal orifices. This may not be true for all multi-orifice catheters. Johans used a multi-orifice catheter with 15 orifices spaced along the distal 10-cm segment (8). The orifices were 2.5-mm in diameter (T. Johans, personal communication). Johans found that the ECG trace arose from the proximal orifice. Number of orifices, orifice size, or other factors may determine the site of origin of the ECG complex in multi-orifice catheters.

Our results support the *in vitro* findings of Bunegin et al. (4) that the choice of venous catheter may have clinical implications for aspiration of venous air. We found that only the Bunegin-Albin multi-orifice catheter allowed retrieval of most of the dose of intravenously infused air and resuscitation from a lethal dose of venous air in most dogs. The RA port of the Swan-Ganz catheter and the Sorenson single-orifice catheters were largely ineffective for either purpose. We did not determine whether the amount of air retrieved with the Bunegin-Albin catheter was greater because it had multiple orifices or because it had the lowest resistance of the catheters studied (Table 1). However, in the study by Bunegin et al. (4), the less effective single-orifice catheter had the same resistance as did the multi-orifice catheter (M.S. Albin, personal communication).

Bunegin et al. (4) injected air into the SVC and placed their heart model at various angles from the horizontal position. Their experimental model thus resembled the situation that exists during a sitting craniotomy. Our experimental model more closely re-

sembles clinical situations in which the patient is not sitting and air emboli enter the heart via the IVC (9,10). The dogs had air injected via the femoral vein and were in the prone rather than the vertical position. Thus air emboli entered the RA via the IVC orifice and might be less likely to float up into the SVC near the vicinity of the proximal orifice of the Bunegin-Albin catheter or the Sorenson SVC catheter. Nonetheless, the Bunegin-Albin catheter retrieved more air than did the Sorenson catheter in closest proximity to the IVC or the Sorenson catheter situated in the SVC. We conclude, therefore, that the Bunegin-Albin multi-orifice catheter is the appropriate catheter for the patient undergoing a craniotomy in the sitting position.

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The Effects of Age, Epinephrine, and Operative Site on Duration of Caudal Analgesia in Pediatric Patients

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Warner MA, Kunkel SE, Offord KO, Atchison SR, Dawson B. The effects of age, epinephrine, and operative site on duration of caudal analgesia in pediatric patients. *Anesth Analg* 1987;66:995-8.

The effects of age, operative site (penoscrotal or inguinal), and the addition of epinephrine 1:200,000 to bupivacaine on duration of postoperative analgesia after caudal block were prospectively and blindly evaluated in 341 children aged 13 months to 17 yrs. At the conclusion of the surgical procedures under halothane/N₂O/O₂ anesthetics (n = 419), caudal blocks were performed with 0.5 ml/kg of either 0.25% bupivacaine or 0.25% bupivacaine with 1:200,000 epinephrine injected at a rate of 0.5 ml/sec. The duration of

analgesia was noted by parents or nurses who had been instructed how to identify, in a standard manner, the onset of postoperative pain. The mean duration of analgesia was significantly longer in young children ($P < 0.001$), in children having penoscrotal operations ($P < 0.001$), and when epinephrine was added to bupivacaine ($P < 0.001$). There were no major complications. The authors conclude that duration of analgesia is significantly influenced by age, operative site, and the addition of epinephrine 1:200,000 to bupivacaine.

Key Words: ANESTHESIA, PEDIATRIC. ANESTHETIC TECHNIQUE, EPIDURAL—CAUDAL.

Caudal anesthesia for postoperative pain relief in children after penoscrotal or inguinal operations is technically simple and safe for both inpatients and outpatients. The duration of analgesia in these patients after caudal injection of bupivacaine has been reported as ranging from 4 to 12 hr, based on the time from injection until pain medication was needed (1-3). In our practice, we noticed prolonged postoperative analgesia after caudal block in children less than 5 years old and in children of all ages receiving 0.25% bupivacaine with epinephrine 1:200,000 dilution compared with 0.25% bupivacaine without epinephrine. Therefore, we studied a large number of pediatric patients undergoing penoscrotal and lower inguinal procedures to determine the effects of adding epinephrine 1:200,000 to 0.25% bupivacaine, as well as the effects of age and the operative site, on the duration of postoperative analgesia.

Methods

From February 1983 to February 1985, 341 children aged 13 months to 17 yr underwent 419 penoscrotal or lower inguinal procedures and received caudal anesthesia for postoperative analgesia. Of these, 182 procedures (43%) were performed on an outpatient basis.

All anesthetics were given by three anesthesiologists. In the immediate preoperative period, each anesthesiologist described in a standard fashion to the children (if they were old enough to understand) and their parents the caudal anesthetic, its role in providing postoperative analgesia, and methods to evaluate the presence or absence of postoperative pain in the inguinal or penoscrotal area. These methods differed between younger, nonverbal children and older children who could talk. In nonverbal children, parents were asked to note the time of onset of apparent discomfort in the operated area. Specific examples included a crying child pulling on his diaper and a child who would cry when his hips were actively flexed or extended. In older, verbal children, parents were asked to note the time of onset of discomfort in the operative area as described by the unprompted child. Pediatric nurses were similarly instructed to note the time of pain onset in children who were inpatients.

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Table 1. Duration of Analgesia (hr) in Pediatric Males Using 0.25% Bupivacaine with and without 1:200,000 Epinephrine

	Lower inguinal						Penoscrotal					
	1-5		6-10		11+		1-5		6-10		11+	
Age (yr)												
Epinephrine	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
n	29	40	12	17	2	2	95	108	35	44	10	20
Median	18.5	7.9	9.5	6.0	6.1	5.1	23.5	9.8	10.8	7.5	8.6	6.2
Mean	18.0	8.1	9.1	6.5	6.1	5.1	23.2	10.0	10.6	7.8	8.6	6.3
SD	3.2	1.5	1.8	1.1	0.9	0.5	3.6	1.9	2.1	1.7	1.5	1.2
Range	12.0-25.0	5.8-11.8	5.8-12.0	5.0-8.8	5.5-6.8	4.8-6.5	15.6-30.5	6.5-15.8	6.0-16.2	4.8-12.8	6.0-11.8	4.0-9.8

No child received preoperative medication or perioperative narcotics. Anesthesia was induced with either rectal methohexital or N₂O/O₂/halothane and maintained with N₂O/O₂/halothane. To standardize the calculation of postoperative analgesic duration, all caudal blocks were performed at the conclusion of surgery. Patients received caudal injections of either 0.25% bupivacaine to which epinephrine had been added just before injection to make a 1:200,000 epinephrine solution or 0.25% bupivacaine without epinephrine in a dose of 0.5 ml/kg. All injections were performed with 23-gauge, 2.5-cm needles. The injection rate was 0.5 ml/sec.

All blocks were performed either by one of the three anesthesiologists or by residents under their supervision. The children were not randomized to receive bupivacaine with or without epinephrine. However, the anesthesiologists were randomly assigned to provide care for these children. Two anesthesiologists used bupivacaine without epinephrine in all 234 of their patients' procedures and one used bupivacaine with epinephrine in all 185 of his patients' procedures.

Data on times of onset of discomfort in the operative area, as noted by observers (either parents or nurses) who were unaware of the anesthetic used, were collected 36-48 hr postoperatively. These data were submitted to an analysis of variance using a three-way factorial design. The three factors were 1) age group (1-5, 6-10, or 11+ years), 2) operative site (lower inguinal or penoscrotal), and 3) use of epinephrine (yes or no). Two- and three-way interactions were analyzed. In addition, using a more conservative analytic approach, age groups were compared regarding use of epinephrine and operative site by two-sample *t*-tests. *P* < 0.05 was considered statistically significant.

Results

A summary of the patient groups is presented in Table 1. All patients were male with ages ranging from 13 months to 17 years.

The duration of analgesia was significantly influenced by the main effects of age, operative site, and the addition of epinephrine to bupivacaine. In general, the mean duration of analgesia increased with decreasing age in penoscrotal procedures and with the addition of epinephrine. The effect of epinephrine on prolongation of analgesia decreased with increasing age as evidenced by the two-way interaction between age groups and epinephrine use. To a lesser degree, the effect of operative site (duration of analgesia was longer after penoscrotal than inguinal procedures at comparable ages and caudal injectate) diminished with increasing age, as evidenced by the two-way interaction between operative site and age groups. The effect of epinephrine was not specific to operative site. The significance of the three-way interaction term was weak.

Further analysis, using two-sample *t*-tests, showed similar highly significant effects of operative site (penoscrotal more than lower inguinal) and the addition of epinephrine to bupivacaine (yes more than no) on duration of analgesia.

There were no major complications of the caudal block. Minor complications included nausea and/or vomiting in 33 (8.0%) patients and transient weakness of the lower extremities in 10 (2.4%) patients. In most cases, children who preoperatively were able to control micturition were able to void within 2 hr of the caudal injection. Only two children were unable to void within 5 hr of the injection: one, given bupivacaine with epinephrine, voided within 8 hr; the other, given bupivacaine with epinephrine, voided within 6 hr.

Discussion

In adults, duration of analgesia after epidural blocks with bupivacaine increases up to 25% with the addition of 1:200,000 epinephrine (4). A similar increase in postoperative analgesia was found in our patients more than 5 years old. In contrast, a much larger increase in duration of postoperative analgesia was found in our children less than 5 years old. This in-

crease was unrelated to differences in operative site (penoscrotal vs inguinal).

The mechanism(s) of the marked prolongation of postoperative analgesia in our younger children is unclear. Possible explanations include age-related anatomic differences that may result in a more cephalad sensory block of the volume (0.5 ml/kg) of anesthetic injected in younger compared with older children. Conventional dogma suggests that the more cephalad the anesthetic level obtained, the longer the duration of analgesia at the original level of sensory loss, in this case the sacral nerves. This is supported by our findings that children having lower inguinal procedures had shorter analgesic periods than did children of similar ages undergoing penoscrotal procedures. We did not, however, attempt to distinguish levels of sensory loss in our young patients. In addition, there may be a decreased tendency of younger children to complain of pain or of their parents to recognize the onset of the pain.

Our injectate volume of 0.5 ml/kg was derived from the modified formula proposed by Takasaki et al. (5): $0.05 \text{ ml} \times \text{body weight (kg)} \times \text{spinal segments}$. For the operations performed in our study, a 10-dermatome segment (to approximately T10) provided satisfactory analgesia, although it is clear that the analgesic period was longer in penoscrotal (sacral innervation) compared with lower inguinal (lumbar and lower thoracic innervation) procedures. Other formulas for determining volume of injectate have been based on patient age or length of the spinal column (6). There is a correlation between body weight, age, and spinal column length until 2 to 4 years old (7). Thereafter, these parameters are nonlinear. As a consequence, a volume that is calculated on the basis of weight will generally result in a more cephalad level of anesthetic in a younger as compared to an older child.

There is also an age-related anatomic difference in the epidural fat of children. During early childhood, the epidural fat is loosely packed and gelatinous (8). The resultant texture of tissue in the epidural space progresses to a tightly packed, fibrous structure by early adulthood. The loose structure of the epidural fat of a young child may allow a greater spread of a given injectate volume than the tight, fibrous fat in an older child or adult.

The pharmacokinetics of bupivacaine absorption from the caudal epidural space are similar in children and adults (9,10). Because of the larger volume of distribution in infants (11) and young children, however, the terminal half-life is slightly prolonged. This difference should not be causally related to the prolongation in duration of postoperative analgesia seen

in younger compared with older children. The addition of 1:200,000 epinephrine does not significantly alter bupivacaine pharmacokinetics in children after caudal anesthetics (12).

We recognize that possible sources of error in this study include the imprecise end point of postoperative analgesia and possible differences in pain perception between young and older children. Although parents were given specific, standardized examples for evaluating the onset of pain, cries of young, non-verbal children interpreted by parents to mark the end of analgesia may have been cries of hunger, nausea, or fear. Our data suggest, however, that an imprecise end point of analgesia may not have caused a major error in our study's results. The duration of analgesia changed gradually during the transition from non-verbal (1-2 years old) to early verbal (3-5 years old) ages. If imprecise parental evaluation of pain onset created a major error, abrupt changes in the durations of analgesia during the transition period would have been expected. Differences in pain perception to standard surgical procedures between young and older children has not been well documented to our knowledge. However, young children do have pain after penoscrotal procedures (13).

In summary, the addition of 1:200,000 epinephrine to bupivacaine, young age, and operations performed in areas with sacral innervation were factors that resulted in prolonged postoperative analgesic periods after caudal blocks with dosages based on weight in children undergoing penoscrotal or lower inguinal procedures.

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Analgesic and Cardiorespiratory Effects of Epidural Sufentanil and Morphine in Humans

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VAN DER AUWERA D, VERBORGH C, CAMU F.
Analgesic and cardiorespiratory effects of epidural
sufentanil and morphine in humans. *Anesth Analg*
1987;66:999-1003.

Thirty patients undergoing abdominal surgery were randomly assigned postoperatively into two groups for a double-blind evaluation of the analgesic potency and cardiorespiratory effects of either 50 μ g sufentanil or 5 mg morphine injected epidurally. After sufentanil injection, good postoperative analgesia was obtained, with a linear analog score (LAS) of less than 5 starting 5 min after injection and lasting for more than 6 hr. Linear analog scores obtained during coughing (LASC) and during movement (LASM) were less than 5 after 10 min and lasted for more than 4 hr. Respiratory rate decreased significantly for 2 hr after sufentanil injection. After morphine, pain relief started after 20 min

and lasted for more than 12 hr. Respiratory rate decreased after 30 min. Sedation was greater after sufentanil than after morphine. P_{aCO_2} , which increased significantly 1 hr after sufentanil, did not change after morphine. Peak expiratory flow significantly improved for 2 hr after both sufentanil and morphine, whereas forced vital capacity improved for 4 hr after sufentanil and 8 hr after morphine administration. Forced expiratory volume did not change with either drug. It is concluded that 5 mg morphine injected epidurally provides longer lasting analgesia than does 50 μ g sufentanil, but that in the first hours analgesia is better after sufentanil. Injection of either drug was accompanied by remarkable cardiovascular stability.

Key Words: PAIN—POSTOPERATIVE. ANALGESICS—morphine, sufentanil. ANESTHETIC TECHNIQUES—EPIDURAL.

The analgesic effects of epidurally injected morphine have been well studied (1,2). Sufentanil, a synthetic and highly selective μ -ligand (3-5), has been used epidurally to relieve postoperative pain (6,7), but a comparative study with morphine has not been published. Similarly, although the cardiovascular and respiratory effects of epidural morphine for postoperative pain relief have been extensively studied (8-10), these effects of epidurally injected sufentanil have been only partially documented (6). We therefore compared the analgesic potency and cardiorespiratory effects of 50 μ g sufentanil and 5 mg morphine administered epidurally in a double-blind randomized study. The choice of these dosages was made on the basis of previous reports regarding the clinical efficacy and safety of morphine (11) and sufentanil (6,7).

Methods

The study was carried out on 30 patients scheduled for abdominal surgery. None had any allergies or systemic disease; all were ASA category I or II. Any medication being given was discontinued at least 48 hr before surgery. The study protocol was approved by the Ethical Commission of the Faculty of Medicine and all patients gave informed consent. All patients received 10 mg diazepam orally and 0.5 mg atropine IM 90 and 30 min before surgery, respectively. In the operating room, an IV catheter was inserted and a single-use 18-gauge epidural cannula was placed through a 17-gauge thin wall Tuohy needle placed at T6-7 for high abdominal surgery, or at T11-12 or L1-2 for lower abdominal surgery. The patients were then placed in the supine position. A 20-gauge indwelling Teflon catheter was inserted into the radial artery for sampling and for monitoring arterial pressure. After preoxygenation and precurarization, general anesthesia was induced with etomidate, 0.3 mg/kg followed by succinylcholine, 1 mg/kg to facilitate tracheal intubation. Anesthesia was maintained either with enflurane (1-3%) or halothane (0.5-1%) and the patients were ventilated with an O_2/N_2O mixture with

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Table 1. Patient Demographics

	Sufentanil group	Morphine group
Male/female	8/7	7/8
Age (yr)	53.4 ± 4.3 (20-73)	59.6 ± 3.9 (26-77)
Weight (kg)	66.4 ± 3.0 (44-92)	63.0 ± 3.0 (44-86)
Height (cm)	165.3 ± 3.1 (150-186)	165.6 ± 2.5 (148-182)
Duration of anesthesia (min)	203.6 ± 16.7 (120-315)	174.0 ± 17.6 (95-325)
Time between end of anesthesia and epidural injection (min)	97.0 ± 10.4 (30-150)	89.3 ± 8.2 (30-160)
Procedure		
Cholecystectomy	7	5
Vagotomy	2	1
Splenectomy	—	1
Colectomy	4	5
Anterior resection rectum	1	1
Hysterectomy	1	—
Laparotomy	—	2
	15	15

Mean values ± SEM with range in parentheses.

a FiO_2 of 0.3 to 0.5. No opioids were used, nor were local anesthetics injected into the epidural catheter.

After surgery the patients were transported to the recovery room where, as soon as they were mentally alert and able to cooperate fully, they were given epidural injections of either 50 μ g sufentanil or 5 mg morphine diluted in 10 ml saline. The patients were randomly assigned into two groups in a double-blind fashion. The catheter was flushed with 2 ml physiologic solution. Heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), and pain assessed by patients by means of a linear analog scale (LAS) (12) were recorded first before injection, then at 5, 10, 20, 30, 45, 60, 90, and 120 min after injection, and then every hour for 12 hr after that. Pain intensity was evaluated at rest (LAS), on coughing (LASC), and after active movement (LASM). Sedation was assessed by a physician using a categorical scale ranging from 0 to 3, with an increasing score matching sedation. Spirometric measurements of forced vital capacity (FVC), peak expiratory flow (PEF), and forced expiratory volume (FEV_1) were made with patients in a 45° seated position before injection and at 1, 2, 4, 8, and 12 hr afterward. Blood gas tensions were measured before spirometry. The patients were encouraged to remain in the study protocol for 12 hr after epidural administration of the analgesic. If pain was insufficiently controlled, the patient was given intramuscular analgesics. The scores of pain intensity at the time of such "rescue" were entered for the remaining observation periods in the study. At the end of the study period, patients were given supplementary analgesics on demand. Cardiorespiratory monitoring was continued for 72 hr postoperatively. All

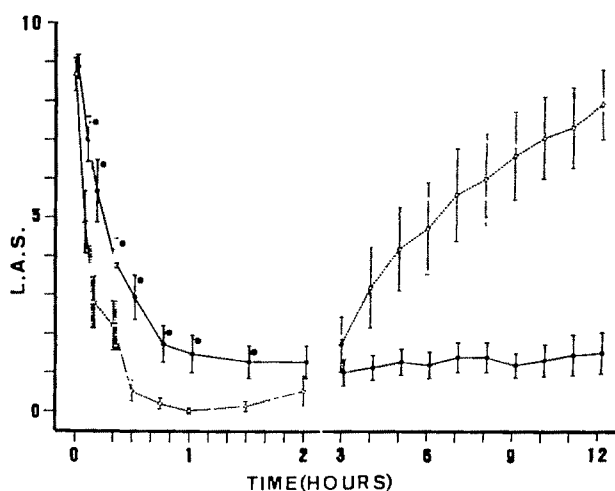


Figure 1. Effect of 50 μ g epidural sufentanil (-----) or 5 mg epidural morphine (—) on linear analog pain scale at rest (means ± SEM). * Solid circles indicate significant differences between groups. L.A.S., linear analog scale.

data are expressed as mean values ± SEM and were analyzed using paired and unpaired *t*-tests for parametric data, the Wilcoxon test, and Mann-Whitney U-test for nonparametric data. $P < 0.05$ was accepted as indicative of statistical significance.

Results

The two groups of patients were comparable in age, weight, height, duration of anesthesia, and time between the end of anesthesia and the need for epidural injection of an opiate (Table 1).

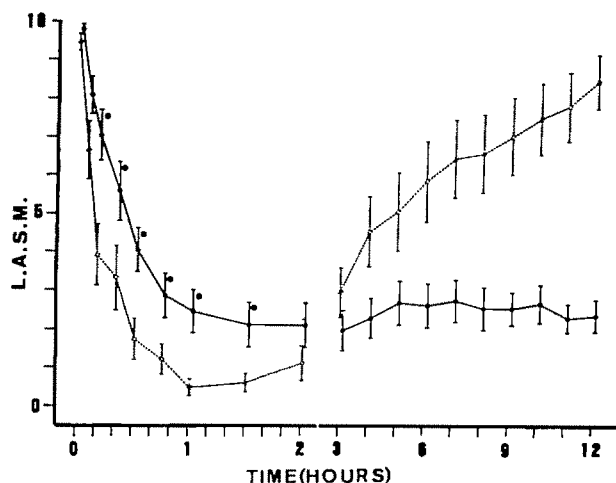


Figure 2. Effect of 50 µg epidural sufentanil (-----) or 5 mg epidural morphine (—) on linear analog pain scale associated with active movement (means $\pm$ SEM). * Solid circles indicate significant differences between groups. L.A.S.M., linear analog scale after active movement.

Effect on Postoperative Pain Relief and Sedation

Epidurally injected sufentanil relieved pain at rest (LAS <5), starting 5 min after the injection and lasting for more than 6 hr. Good postoperative analgesia with coughing (LASC, <5) and active movement (LASM, <5) started after 10 min and lasted more than 4 hr (Fig. 1 and 2). After epidural morphine, LAS decreased after 20 min, with LASC and LASM decreasing after 30 min. Analgesia measured as LAS, LASC, and LASM lasted for more than 12 hr. LASC and LASM scores were similar with both narcotics.

Maximal analgesia, seen 60 min after sufentanil and 3 hr after morphine administration, was significantly better with sufentanil. After 60 min, 14 of 15 patients given sufentanil were pain-free, whereas after 3 hr 7 patients given morphine still had some pain. Neither dermatomal analgesia nor motor block occurred. Sufentanil provided significantly more profound analgesia than did morphine from 5 min until 90 min after injection (Fig. 1 and 2). Sedation was greater after sufentanil than after morphine. The onset of sedation after sufentanil was nearly immediate and lasted for 3 hr, whereas after morphine sedation, though not as great, sedation lasted for more than 12 hr.

Hemodynamic Effects

Differences between the lowest levels of MAP and HR after epidural injection and baseline control values were similar in both groups. Mean arterial pressure decreased at most by 8% after 30 min after sufentanil compared with 15% after 4 hr after morphine. The

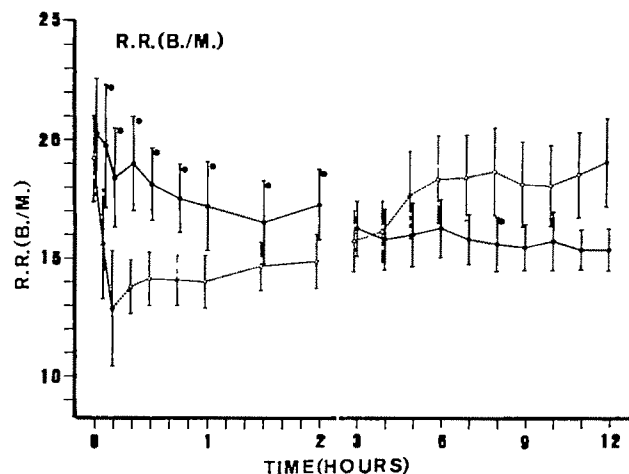


Figure 3. Changes in respiratory rate after 50 µg epidural sufentanil (-----) or 5 mg epidural morphine (—) (means $\pm$ SEM). * Solid circles indicate significant differences between groups. R. R., respiratory rate; B./M., breaths/min.

maximal decrease in HR (5%) occurred 10 min after sufentanil compared with a 7% decrease after 20 min in the morphine group. None of these changes were statistically significant.

Ventilatory Effects

After epidural injection of sufentanil, RR significantly decreased, to a maximal decrease of 30% below preinjection value for 3 hr (Fig. 3), an effect that became apparent after 5 min. Two patients given sufentanil experienced a severe respiratory depression (RR, 4 breaths/min) within 10 min of injection. In both there was, however, spontaneous recovery of respiratory rate.

After morphine injection, a significant decrease in RR became apparent after 30 min and lasted for more than 12 hr, the maximal decrease averaging 23%. In the morphine group we observed no respiratory depression within 12 hr after injection. Respiratory rate was significantly lower in the sufentanil group than it was in the morphine group until 2 hr after injection. After 8 hr, however, the situation changed and RR was significantly lower in the morphine group than in the sufentanil group.

Arterial carbon dioxide tension (PaCO_2) increased significantly above preinjection values 1 hr after sufentanil (Table 2), whereas changes in PaCO_2 were not significant after morphine. Also, no significant differences were detected between both treatment groups.

Peak expiratory flow was significantly improved for 2 hr after both sufentanil and morphine (Fig. 4).

Table 2. Changes in Arterial Carbon Dioxide Tension (mm Hg) after Epidural Sufentanil or Morphine (Mean Values $\pm$ SEM)

Time	Sufentanil 50 μ g	Morphine 5 mg
Before (hr)	35.7 $\pm$ 1.0	38.6 $\pm$ 1.2
1	38.8 $\pm$ 1.0*	38.6 $\pm$ 1.1
2	36.8 $\pm$ 0.8	38.4 $\pm$ 1.3
4	35.8 $\pm$ 0.9	39.9 $\pm$ 1.4
8	35.8 $\pm$ 1.0	38.6 $\pm$ 1.4
12	35.8 $\pm$ 1.0	36.5 $\pm$ 0.8

* $P < 0.05$; difference vs baseline value (Wilcoxon test).

However, the improvement lasted longer after morphine, except for one point 12 hr after injections. Otherwise the only difference in PEF between the two groups was a greater improvement in PEF 1 hr after sufentanil.

Forced vital capacity improved for 4 hr after sufentanil and for 8 hr after morphine. The difference between the two groups was significant after 2 hr, when FVC was better with sufentanil, but more satisfactory FVC values were observed after 8 hr with morphine.

Forced expiratory volume increased 5% after morphine throughout the entire study period in contrast to an initial decrease after 1 hr and a minimal (2%) improvement after 8 hr in the sufentanil group. However, none of these changes reached statistical significance.

Discussion

Epidurally injected opioids have become very popular in recent years for relief of postoperative pain. The most widely used drug is still morphine, which produces effective long-lasting analgesia but at the cost of a high incidence of side effects (1,13-16). Our findings confirm previous reports on morphine, including the duration of analgesia.

This study indicates that sufentanil 50 μ g administered epidurally produces rapid, effective pain relief during the early postoperative period. Other authors (6,7) suggested that 50 μ g sufentanil might be an "optimal" dose for this purpose. Although respiratory depression, if any, seemed to occur shortly after administration, we believe that epidural sufentanil administration should be restricted to patients in an intensive care unit or in a high-care recovery room only. The rapid onset of respiratory depression after sufentanil administration suggests that it could be related to an extensive systemic uptake immediately after epidural injection. Alternatively, the high liposolubility of sufentanil might allow rapid penetration from the cerebrospinal fluid (CSF) into the cord (17-19).

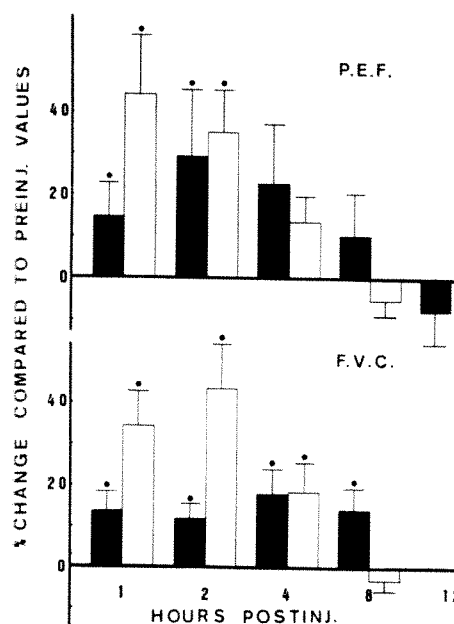


Figure 4. Percent change in pulmonary function tests following epidural administration of 50 μ g sufentanil (white bars) or 5 mg morphine (black bars) (means $\pm$ SEM). * Solid circles indicate significant difference from control. P.E.F., peak expiratory flow; F.V.C., forced vital capacity.

This is different from the delayed respiratory depression seen after epidural morphine, which is due to the cephalad spread in CSF (14,15,20-22). There are earlier reports of an initial transient respiratory depression when lipophilic opiates were given (6,18,19,23-25).

We do not consider the moderate sedation that occurred after sufentanil administration as a side effect. Sedation may be advantageous for patients in the recovery ward: it did not impair communication and spirometric tests could be performed. Other studies, however, report an important degree of sedation (26).

Previous authors have implied that the better the analgesic effect, the better pulmonary function (8-10,27,28). Adequate pain relief allowing sighing and coughing is indeed important for prevention of atelectasis after abdominal surgery. In our study the analgesic effect was greatest during the first 6 hr after epidural sufentanil. This correlated well with the observation that PEF and FVC were best during this period. The improvement in spirometric tests lasted longer after morphine but did not correlate with the analgesic effect. The inability of patients to cooperate fully after morphine may have contributed. The slight impairment of FEV₁ after epidural sufentanil may have resulted from the greater sedation or from bronchospasm mediated by histamine release.

In conclusion, 5 mg epidural morphine provided analgesia permitting coughing and active movement for >12 hr after abdominal surgery, whereas 50 μ g epidural sufentanil, though providing a more intense degree of analgesia, effectively relieved pain for only 6 hr. PaCO_2 was not adversely affected after either narcotic, despite the decrease in respiratory rate observed in both groups. Epidural injection of either drug was accompanied by remarkable cardiovascular stability.

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Erythrocyte Fragility Screening Is Not a Tool for Diagnosis of Human Malignant Hyperthermia

Philip Kistler, BS, Jeffrey E. Fletcher, PhD, and Henry Rosenberg, MD

KISTLER P, FLETCHER JE, ROSENBERG H. Erythrocyte fragility screening is not a tool for diagnosis of human malignant hyperthermia. *Anesth Analg* 1987;66:1004-7

The fragility of erythrocytes from 21 patients undergoing in vitro skeletal muscle contracture testing for malignant hyperthermia (MH) susceptibility was examined. Osmotic fragility was determined by the degree of hemolysis in buffered saline solutions of decreasing osmotic strength. Halothane-induced fragility was determined in an isotonic solution containing increasing percentages of halothane saturated solution. The effects of six different incubation conditions prior to performing fragility tests were examined

in an attempt to optimize discrimination of MH susceptible patients, including the following: 1) no preincubation; 2) 24-hr incubation at 4°C; 3) 72-hr incubation at 4°C; 4) 24-hr incubation at 37°C; 5) 24-hr incubation at 22°C with plasma from an MH-susceptible patient; and 6) 24-hr incubation at 22°C with plasma from a normal patient. Despite examining six different incubating conditions and the two methods of hemolysis induction, no differences in erythrocyte fragility were detected between patients diagnosed as MH susceptible or normal. Erythrocyte fragility testing is not useful for diagnosing MH susceptibility.

Key Words: HYPERTHERMIA—malignant.

Malignant hyperthermia (MH) is a syndrome characterized by temperature elevation, muscle rigidity, rhabdomyolysis, and increased muscle metabolism (1-4), with a mortality rate of approximately 10% (5). Malignant hyperthermia is triggered by drugs used in anesthesia, most notably halothane and succinylcholine (1-4). The diagnosis of MH is currently made by in vitro skeletal muscle contracture testing utilizing halothane and caffeine (6,7). The contracture test involves a skeletal muscle biopsy and labor intensive procedures that are available in only a few specialized centers (7). A simple blood test, if capable of identifying MH susceptible patients, would be less invasive and could be performed by a larger number of laboratories.

Screening for MH susceptibility with erythrocyte osmotic fragility tests is effective in swine. The erythrocytes of pigs susceptible to MH have a greater osmotic fragility than do those from normal swine (8-12). However, similar studies involving human erythro-

cytes have demonstrated either increased, decreased, or no difference in osmotic fragility of erythrocytes from MH-susceptible patients compared with normal subjects (7,13-16).

The present study tests several conditions to optimize the discrimination between MH-susceptible and normal individuals. Halothane was used in some studies, as it is a potent triggering agent of MH capable of inducing hemolysis (16,17). Incubations at 4 and 37°C were performed to detect changes in fragility that may reflect a greater instability in the erythrocyte plasma membrane of MH-susceptible patients. Incubation at 37°C for 24 hr was performed because it is used to discriminate other disorders, such as pyruvate kinase deficiency (18) and thus might reveal differences between normal and MH-susceptible populations. Plasma from patients diagnosed as being MH-susceptible or normal by the in vitro skeletal muscle contracture test was incubated with erythrocytes to determine whether soluble factors may be present in plasma that might cause detectable changes in fragility.

Methods

Approval of the Hahnemann University Hospital Human Studies Committee was granted for this study. Venous blood was collected in heparinized tubes from patients prior to the skeletal muscle biopsy. Patients

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were diagnosed as MH-susceptible or normal by the halothane and caffeine contracture tests as previously described (19). If any one of the 6–8 muscle strips tested with halothane 3% developed a contracture response ≥ 0.7 g, or if either of two strips tested with caffeine 2 mM developed a contracture response >0.3 g, then the patient was considered MH-susceptible. On this basis, 11 patients were MH-susceptible and ten were nonsusceptible. The MH-susceptible patients were further subdivided according to the strength of contracture to halothane 3% to establish a population with an extreme responsiveness to halothane. A mean contracture of ≥ 1.0 g in the 6–8 strips tested with halothane was designated as MH++ (3 patients). Those patients positive for MH, but with a mean contracture <1.0 g were designated MH+ (8 patients). Patients negative for MH by the criteria described above were labeled MH–. Not all tests were done on all samples from all patients. The number of patients tested is indicated in each table.

The blood specimens were maintained at room temperature and processed within 1 hr of collection by centrifugation at $1000 \times g$ for 5 min. The plasma from some patient specimens was then removed and frozen at -20°C for later use. The erythrocytes were resuspended in phosphate-buffered saline of physiologic osmolality (0.9% buffered saline solution) (18) and centrifuged. The supernatant was then discarded. This washing procedure was repeated until the supernatant was visually free of hemoglobin, or for a minimum of three times. The final pellet was termed packed erythrocytes.

The solutions for the osmotic fragility experiments were prepared as described by Dacie and Lewis (18). The osmotic fragility test involved pipetting 4.0 ml of the appropriate solution into a test tube and then adding 10 μl of packed erythrocytes to the tube. The test tubes were thoroughly mixed and incubated at room temperature for 30 min. The tubes were then centrifuged at $1000 \times g$ for 5 min and the supernatant read spectrophotometrically for absorbance at 540 nm. The results were compared with a sample representing 100% hemolysis (10 μl of erythrocytes in the appropriate amount of distilled water) to obtain a figure for percent hemolysis of the sample as previously described (16,17). The median corpuscular fragility (MCF) was estimated as the concentration of NaCl causing 50% hemolysis (18).

The halothane fragility studies were conducted by preparing a saturated solution of halothane (16,17). This was accomplished by the addition of 20 ml of liquid halothane to 400 ml of the 0.9% buffered saline solution contained in a 500-ml brown stoppered glass bottle. The solution was continuously stirred at 37°C

Table 1. Osmotic Fragility of Human Erythrocytes Determined on Preparations Incubated at 4°C for 0, 24, or 72 Hours before Testing

	Period of incubation		
	0 hr MCF ($\bar{X} \pm \text{SEM}$)	24 hr MCF ($\bar{X} \pm \text{SEM}$)	72 hr MCF ($\bar{X} \pm \text{SEM}$)
MH–	0.44 ± 0.01 (10)	0.45 ± 0.01 (9)	0.50 ± 0.01 (8)
MH+	0.44 ± 0.01 (8)	0.46 ± 0.01 (7)	0.49 ± 0.01 (7)
MH++	0.47 ± 0.03 (3)	0.45 ± 0.03 (3)	0.48 ± 0.03 (3)

Results reported as % NaCl at the MCF. The groups were compared within each incubation period by a one-way analysis of variance ($P < 0.05$). None of the comparisons were found to be significantly different. n is shown in parentheses.

for at least 8 hr prior to testing. The aqueous phase within this bottle was designated as the 100% saturated halothane solution. Ten microliters of packed erythrocytes were added to 0.9% buffered saline solution, and the appropriate volume of halothane saturated solution was then added to achieve the percentages previously described for a HEPES-based buffer (16). The 10-ml test tubes were stoppered immediately after the addition of the halothane saturated solution. The tubes were thoroughly mixed and incubated for 30 min at 37°C . After centrifugation, the degree of hemolysis was determined as described above. The estimate of the concentration of halothane saturated solution causing 50% hemolysis was termed the median corpuscular fragility due to halothane (MCFH).

In some cases aliquots of the packed erythrocytes were incubated at 4 or 37°C for 24 or 72 hr before being rewashed and tested for osmotic and halothane-induced fragility. In another study, the MH++ and MH– plasma incubations were performed using the frozen plasma specimens described above. Each plasma sample was first thawed at room temperature and then vortexed to ensure thorough mixing. The plasma was then mixed with equal portions of packed erythrocytes and allowed to incubate for 24 hr at room temperature prior to washing and the fragility tests.

Results

The MCF value for our MH– samples (Table 1) was comparable to that of established normal values (18). The standard osmotic fragility test was performed on erythrocytes from three patient populations (MH–, MH+, MH++) after three incubation periods (0, 24, 72 hr) at 4°C . No significant differences in MCF were observed among the three patient populations after any of the three incubation times (Table 1).

Halothane-induced fragility was also examined after the three incubation periods at 4°C (Table 2). The MCFH values for MH– samples on day one were

Table 2. Halothane-Induced Fragility of Human Erythrocytes Determined on Preparations Incubated at 4°C for 0, 24, or 72 Hours before Testing

	Period of incubation		
	0 hr MCFH ($\bar{X} \pm \text{SEM}$)	24 hr MCFH ($\bar{X} \pm \text{SEM}$)	72 hr MCFH ($\bar{X} \pm \text{SEM}$)
MH-	52 $\pm$ 2 (9)	47 $\pm$ 4 (8)	44 $\pm$ 5 (8)
MH+	42 $\pm$ 5 (6)	44 $\pm$ 5 (6)	41 $\pm$ 4 (6)
MH++	52 $\pm$ 2 (3)	52 $\pm$ 6 (3)	39 $\pm$ 14 (3)

Results reported as percent of a saturated halothane solution at the MCFH (50% hemolysis point). The groups were compared within each incubation period by a one-way analysis of variance ($P < 0.05$). None of the comparisons were found to be significantly different.

n is shown in parentheses.

comparable to values obtained by Tolpin et al. (15). There were no significant differences among the three patient populations at any of the three incubation periods (Table 2).

The osmotic fragility and the halothane-induced fragility tests were also performed on erythrocytes from two groups of patients (MH-, MH+) after incubation for 24 hr at 37°C (Table 3). The MCF values for the 24-hr incubations at 37°C were within the normal range for that test (18). Again, there were no differences among patient populations in regard to osmotic or halothane-induced fragility.

Plasma samples from one of each patient type confirmed as MH- and MH++ by the halothane contracture test were added to erythrocytes and incubated for 24 hr at room temperature to test whether some soluble component of plasma might be present which would allow discrimination of MH-susceptible and normal patients. These erythrocytes were then tested with the osmotic fragility and halothane-induced fragility tests. Since there were no apparent differences between MH- and MH+ erythrocytes (Tables 1-3), the data from the erythrocytes of one MH+ and three MH- patients were pooled to analyze the plasma effects. No differences were detected in the MCF or MCFH values between erythrocyte preparations incubated with MH- or MH++ plasma (Table 4).

Discussion

The purpose of this study was to determine whether human erythrocytes could be used as a reliable screen for differentiating MH-susceptible from normal patients. We tested a wide variety of approaches, attempting to optimize conditions for discrimination of MH-susceptible patients. In addition, a group with a strong response to halothane was also examined to

Table 3. Osmotic and Halothane-Induced Fragility of Human Erythrocytes Determined after a 24-Hour Incubation at 37°C

	Osmotic fragility (% NaCl) MCF ($\bar{X} \pm \text{SEM}$) (n)	Halothane-induced fragility (% halothane saturated sol.) MCFH ($\bar{X} \pm \text{SEM}$) (n)
MH-	0.51 $\pm$ 0.03 (5)	49 $\pm$ 8 (5)
MH+	0.53 $\pm$ 0.03 (5)	40 $\pm$ 8 (5)

The MH- and MH+ groups were compared by two tailed Student's t -test ($P < 0.05$) within each test (osmotic or halothane-induced fragility) type. Neither of the comparisons were found to be significantly different.

Table 4. Osmotic and Halothane-Induced Fragility of Human Erythrocytes after a 24-Hour Incubation with Either MH- or MH++ Plasma at Room Temperature

	Osmotic fragility (% NaCl) MCF ($\bar{X} \pm \text{SEM}$) (n)	halothane-induced fragility (% halothane saturated sol.) MCFH ($\bar{X} \pm \text{SEM}$) (n)
MH- plasma	0.48 $\pm$ 0.01 (4)	58 $\pm$ 2 (4)
MH++ plasma	0.48 $\pm$ 0.01 (4)	59 $\pm$ 2 (4)

Erythrocytes from three MH- patients and one MH+ patient were tested separately and pooled for each comparison. The two conditions (MH- and MH++ plasma) were compared by two tailed Student's t -test ($P < 0.05$) within each test (either osmotic or halothane-induced fragility) type. Neither of the comparisons were found to be significantly different.

aid in the detection of subtle differences in erythrocyte fragility. The data from this study illustrate that erythrocyte fragility, either osmotically or halothane-induced, cannot be used to screen for MH susceptibility. Exposing erythrocytes to various incubation conditions prior to the fragility tests, including incubation at two temperatures (4°C, 37°C), incubation for increasing time periods (0, 24, 72 hr) and additions of plasma from either MH- or MH++ patients, or the addition of a potent MH triggering agent (halothane) to induce hemolysis all failed to reveal any difference in erythrocyte fragility between MH-susceptible and normal patients. The negative results with MH++ plasma incubations also suggest that there may not be a discriminating factor in fragility testing for MH that is soluble in plasma. We hesitate to generalize this point to all blood components at this time.

Perhaps the lack of any detectable difference in fragility of erythrocytes from humans lies in the membrane characteristics and the very defect believed to be responsible for MH. Elevated levels of phospholipase A₂ activity have been implicated as the defect responsible for MH in both pigs (20,21) and humans (22). Halothane and phospholipase A₂ act in synergy to induce hemolysis of erythrocytes (16,17). Also phospholipase A₂ activity significantly increases the fragility of erythrocytes as determined by osmotic lysis (16,17). Therefore, differences in erythrocyte fragility

should be observed in MH-susceptible and normal patients under the right conditions. We have observed significant levels of free arachidonic acid, a major product of phospholipase A₂ activity, within the porcine erythrocyte membrane (unpublished observations). Therefore, it is understandable that detectable differences between porcine MH-susceptible and normal pigs using erythrocyte fragility are reported. In contrast, we have not observed detectable levels of free arachidonic acid in human erythrocytes (17). If the enzyme responsible for MH is absent from the membrane being assayed, as appears to be the case in human erythrocytes, no differences can be detected by that model, in agreement with the present study.

In summary, erythrocyte fragility testing, either osmotically or halothane-induced, is not useful for the purposes of discriminating between MH-susceptible and normal patients. We do not suggest the use of erythrocytes as the basis for any diagnostic test for human MH because the defect responsible for MH does not appear to be located in human erythrocytes.

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Effects of Lidocaine Infusion on the Sympathetic Response to Abdominal Surgery

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Activation of afferent nerves in the area of surgery is a cause for surgical pain and stress. Intravenous (IV) lidocaine has been shown to inhibit postoperative pain. In the present double-blind study, the effects of a continuous IV infusion of lidocaine (2 mg/min) on the sympathoadrenal stress response to surgery were evaluated in 38 patients scheduled for elective cholecystectomy who were randomly assigned to two groups. In one group, lidocaine infusion was started 30 min before the operation and continued for 24 hr after surgery (n = 18). In the second group (n = 20), saline was infused. The increases in heart rate and blood pressure after tracheal intubation were not significantly different between the groups, but tachycardia and hypertension associated with extubation was prevented in patients given lidocaine. Differences in blood pressure and heart rate between

the two groups were otherwise not significant intra- or postoperatively, nor were differences in blood glucose or plasma catecholamine concentrations during the first 24 hr after skin incision. Urinary catecholamine concentrations did not differ significantly in the two groups during the first postoperative day, but during the second postoperative day urinary output of epinephrine and norepinephrine were significantly less in the group of patients receiving lidocaine infusion. It was concluded that the IV infusion of lidocaine during and after major abdominal surgery suppresses extubation-induced hypertension and tachycardia but does not inhibit the general sympathetic response during the first postoperative day. However, lidocaine infusion reduces urinary output of catecholamines during the second postoperative day, suggesting a more rapid decline in the sympathoadrenal response postoperatively in the experimental group.

Key Words: ANESTHETICS, LOCAL—lidocaine.

It is well recognized that abdominal surgery induces a variety of autonomic reflexes resulting in characteristic endocrine and metabolic responses (1,2). The afferent link of this response to surgical trauma has not been elucidated in detail, although painful stimuli and surgical stress most likely play an important part in activating the neuroendocrine response (3-5). The dominant feature of the efferent link consists of a general increase in sympathetic activity (6,7), with release of norepinephrine from sympathetic nerves and epinephrine from the adrenal glands (7-9).

We have previously shown that intravenous (IV)

lidocaine decreases postoperative pain (10), but it may also suppress cough caused by bronchoscopy and intubation (11,12), circulatory responses to tracheal intubation (13), increased intraocular and intracranial pressure after tracheal intubation (14,15), and extubation laryngospasm (16). To determine whether IV lidocaine also inhibits the autonomic reflexes responsible for the sympathoadrenal response to surgery, we gave lidocaine as a continuous IV infusion during 24 hr and measured its effects on plasma and urine concentrations of catecholamines, on blood glucose levels, and on hemodynamic changes associated with abdominal surgery performed under N₂O-O₂, narcotic and relaxant general anesthesia.

Methods

Thirty-eight patients scheduled for elective cholecystectomy were studied. Each patient gave informed consent, and the experimental protocol was approved by the Regional Ethics Committee. Patients with hepatic, renal, cardiovascular, or hormonal diseases were

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excluded. Preanesthetic medication consisted of 0.05–0.075 mg fentanyl and 2.50–3.75 mg droperidol intramuscularly (IM). Anesthesia was induced with thiopental (4 mg/kg). After the administration of 1 mg pancuronium to prevent fasciculations, succinylcholine (1 mg/kg) was given to facilitate tracheal intubation. After intubation, 5 mg pancuronium was given with additional doses of 1 mg as indicated during surgery. Anesthesia was maintained with N₂O and O₂ and a bolus dose of 0.2 mg fentanyl at the induction of anesthesia, followed by 0.003 mg·kg⁻¹·hr⁻¹. At the conclusion of surgery, 1 mg of atropine followed by 2.5 mg of neostigmine was administered to reverse neuromuscular blockade. In one group of patients (*n* = 18), an IV bolus injection of lidocaine (100 mg; 20 mg/ml) was given 30 min before the skin incision, followed by a continuous IV infusion at 2 mg/min (2 g lidocaine in 500 ml physiologic saline) that was continued for 24 hr after completion of surgery. A second group of patients (*n* = 20) was given a similar infusion of saline, not lidocaine. The infusions were given in a double-blind manner. Blood pressure and pulse rate were monitored every 5 min during surgery using an automatic cuff (Dinamap) and at 1-hr intervals postoperatively. The ECG was monitored in all patients through the entire study. Intravenous infusions were restricted to isotonic saline or Ringer's lactate solutions. No infusions of glucose were given before operation or during the time when blood glucose levels were being measured.

Patients complaining of pain postoperatively were given as many IM injections of 50 mg meperidine as necessary for relief of pain.

A questionnaire about adverse reactions to lidocaine (lightheadedness, tinnitus, perioral numbness, drowsiness, and slurred speech) was filled out by patients on the morning of the first postoperative day.

Heparinized venous blood samples (5 ml) for measurement of glucose levels (glucose oxidase method) were taken 1 hr before surgery; 1 hr after skin incision; 10 min after extubation; and 3, 4, and 8 hr after skin incision.

Catecholamine concentrations

Venous blood samples for catecholamine analysis were drawn into prechilled tubes on ice containing 9 mg EDTA and 6 mg glutathion as antioxidant 1 hr before surgery; immediately before skin incision; 1 hr after skin incision; 10 min after extubation, and 3, 4, 8, and 24 hr after skin incision. The samples were immediately centrifuged for separation of plasma and frozen at -70°C until analysis. Norepinephrine, epinephrine, and dopamine in plasma were measured using

Table 1. Demographic Data in 38 Patients Undergoing Cholecystectomy under General Anesthesia with 24-hour Intravenous Infusion of Lidocaine or Saline

	Saline	Lidocaine
Number	20	18
Age (yr)	49 ± 2	54 ± 2
Sex (F/M)	14/6	12/6
Weight (kg)	72 ± 4	69 ± 4
Duration of surgery (min)	102 ± 8	110 ± 6
Fentanyl during surgery (mg)	0.44 ± 0.03	0.46 ± 0.02
Meperidine (mg)		
First postoperative day	135 ± 23	103 ± 22*
Second postoperative day	73 ± 16	7 ± 3*

Values are mean ± SEM.

**P* < 0.05; **P* < 0.01 vs control group.

a high performance liquid chromatography (HPLC) technique with electrochemical detection (17). Reference values for norepinephrine in our laboratory in unrestrained patients during supine rest are 1.18–2.36 nmol/L (18).

Urine for analysis of catecholamines was obtained during two consecutive 24-hr periods in plastic containers (with 32 ml 5 M HCl added) starting immediately after surgery. At the end of each 24-hr period, the container was shaken firmly and a sample (10 ml) was taken in a polyethylene tube and frozen at -70°C for subsequent analysis using HPLC.

Standard *t*-tests were used to calculate the statistical significance of differences between the groups. Wilcoxon's signed-rank test was used to calculate the statistical significance of changes within groups. Data are expressed as mean ± SEM. Differences resulting in *P* values less than 0.05 were considered statistically significant.

Results

The two groups of patients were similar with regard to age, weight, sex distribution, and the duration of surgery (Table 1). Blood loss in the control group (181 ± 24 ml) and in the lidocaine group (203 ± 32 ml) was also similar. No blood transfusions were required in any patient. The dose of fentanyl given during surgery did not differ between the groups. The need for meperidine was significantly less in the lidocaine group during the first and second postoperative days (Table 1).

The incidence and severity of hypertension and tachycardia after tracheal intubation did not differ significantly between the groups (Fig. 1). After extubation, significant inhibition of increases in heart rate and arterial blood pressure (Fig. 2) was observed in patients given lidocaine. Differences in heart rate and

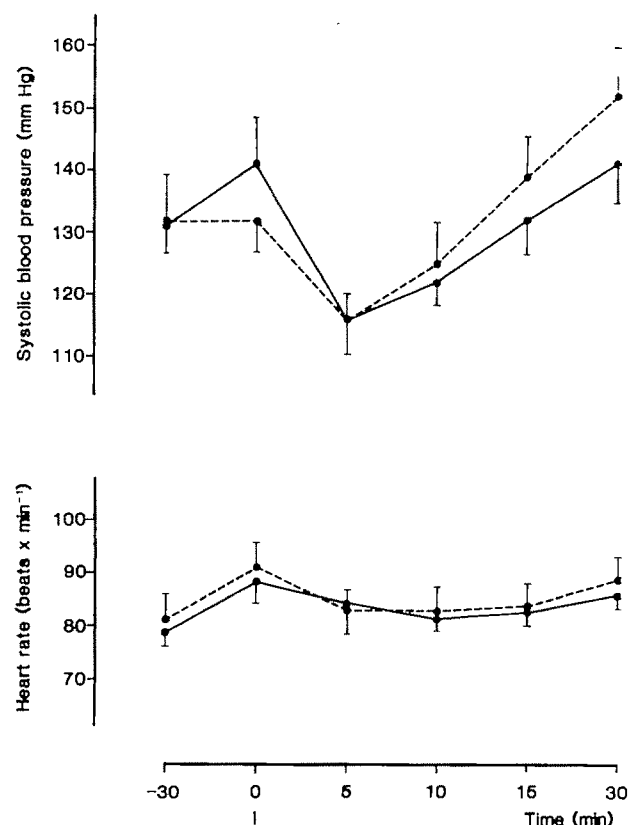


Figure 1. Arterial blood pressure and heart rate during intubation in patients treated with lidocaine (dotted line) and in controls (solid line). Differences were not significant. I, Intubation.

blood pressure in the two groups were otherwise not statistically significant intra- or postoperatively. Blood glucose levels (Fig. 3), plasma concentrations of norepinephrine (Fig. 4), epinephrine (Fig. 5), and dopamine (Fig. 6) were not significantly different in the groups during surgery and for the first 24 hr after the operation.

Urinary concentrations of catecholamines did not differ significantly between the groups during the first day after surgery (Fig. 7). Urinary concentrations of norepinephrine were, however, significantly greater in the control group on the second postoperative day than in the lidocaine-treated group (Fig. 7).

Urinary concentrations of epinephrine were significantly reduced during the second day after surgery in lidocaine-treated patients but not in control patients (Fig. 7). No significant differences were seen between the groups in urinary dopamine levels during the second day (Fig. 7).

The incidence of postoperative nausea and vomiting did not differ significantly in the two groups. Aside from drowsiness in two patients in the lidocaine group, no side effects due to possible lidocaine overdosage were reported.

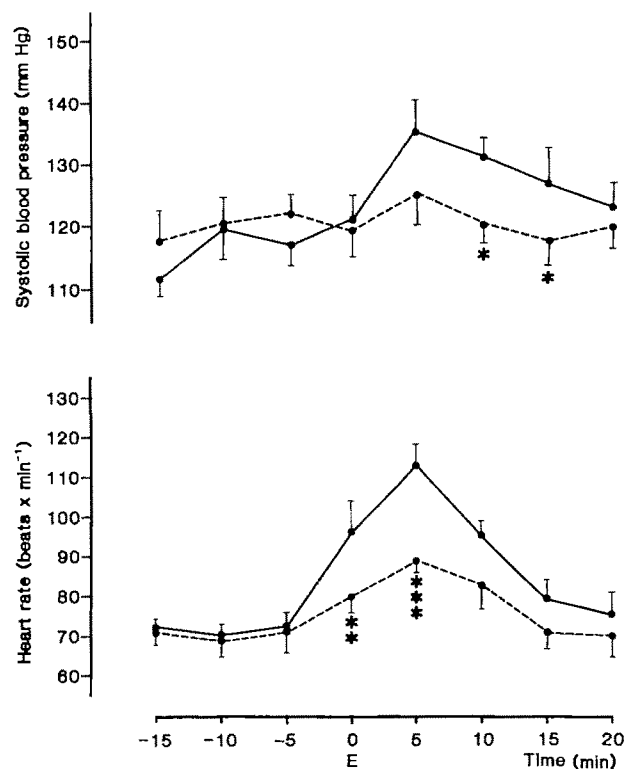


Figure 2. Changes in arterial blood pressure and heart rate following extubation in lidocaine-treated patients (dotted line) and in control patients (solid line). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ as compared with control. E, extubation.

Discussion

Laryngoscopy and tracheal intubation are procedures known to induce reflex cardiovascular effects in anesthetized patients. Such changes include a pressor response as well as tachycardia (19). The cardiovascular changes usually occur in parallel with increased sympathetic activity and increases in plasma levels of norepinephrine and epinephrine (20, 21).

As shown in previous studies, IV bolus injections of lidocaine may suppress the activation of autonomic reflexes secondary to endotracheal manipulations (13). In the present study, lidocaine significantly inhibited increases in heart rate acceleration and blood pressure but had no significant effect on plasma concentrations of catecholamines after extubation. A possible explanation for this difference could be that changes in plasma catecholamine levels are more transient than cardiovascular changes after extubation and that blood samples taken closer to the extubation might have detected changes in catecholamine levels. Moreover, norepinephrine spillover in plasma, which primarily reflects sympathetic nervous activity in skeletal muscle and the splanchnic area, may not necessarily re-

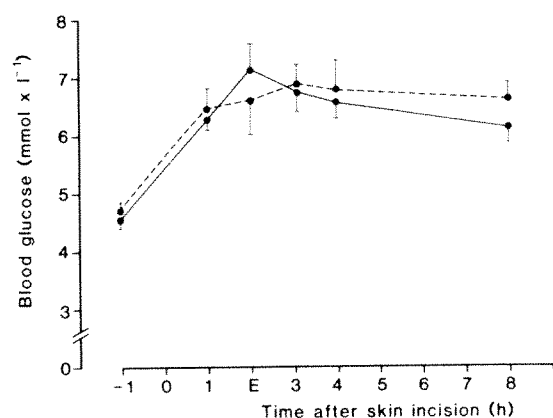


Figure 3. Blood glucose levels during and after surgery in lidocaine-treated patients (dotted line) and in control patients (solid line). Differences between the groups were not significant.

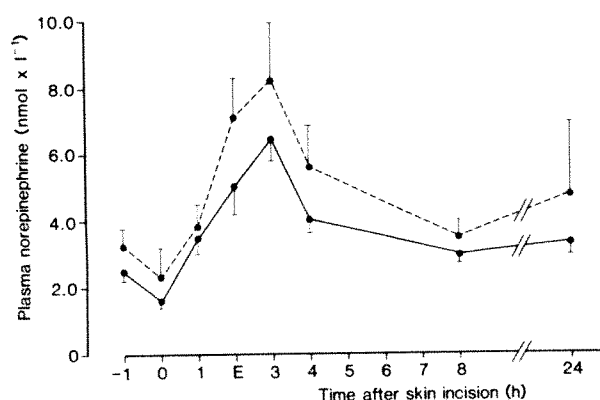


Figure 4. Plasma concentrations of norepinephrine during and after surgery in patients treated with lidocaine (dotted line) and in control patients (solid line). Differences between the groups were not significant.

flect sympathetic output in the heart. The mechanisms of action of IV lidocaine on laryngeal reflexes as reflected by inhibition of hypertension and tachycardia could be due either to attenuation of the activity in afferent C-fibers from the larynx (22) or secondary to central depressant actions (23, 24).

In contrast to extubation, lidocaine infusions did not alter the cardiovascular responses usually seen during and after intubation. In a previous study (25), fentanyl was shown to inhibit the catecholamine release after intubation and surgical trauma. However, doses of fentanyl that did so ($24 \mu\text{g/kg}$) were significantly greater than the doses used in the present study ($3 \mu\text{g/kg}$). However, the possibility cannot be excluded that the low dose of fentanyl given to our patients shortly before intubation might have been sufficient to blunt the cardiovascular effects of intubation and thus mask the possible beneficial effects of lidocaine. Such an interpretation may be supported

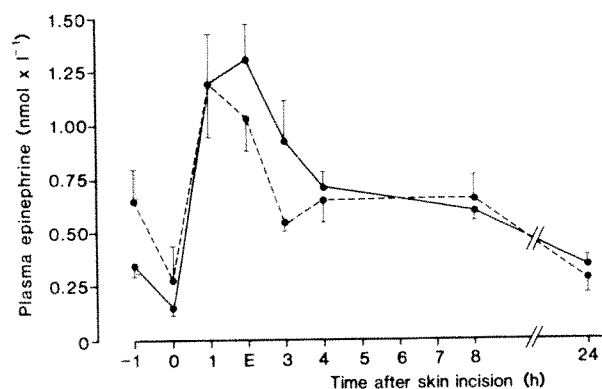


Figure 5. Plasma concentrations of epinephrine during and after surgery in patients treated with lidocaine (dotted line) and in control patients (solid line). Differences between the groups were not significant.

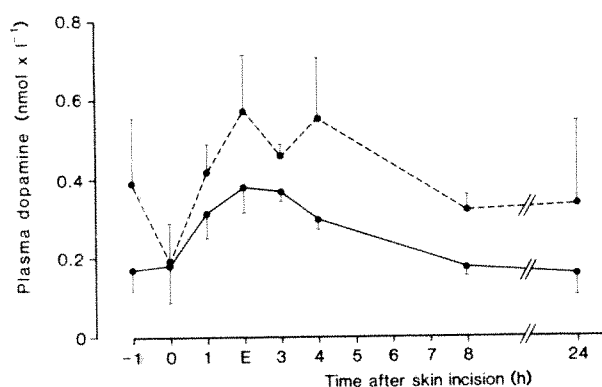


Figure 6. Plasma concentrations of dopamine during and after surgery in patients receiving lidocaine (dotted line) compared to control patients (solid line). None of the differences between the groups were significant.

by the relatively small changes in blood pressure and heart rate seen in the present study after tracheal intubation (Fig. 1) compared to previous reports using inhalation anesthetics for intubation (20, 26). A potential sympathoinhibitory effect of fentanyl could have been further potentiated by the pentobarbital given immediately before intubation (25) as it has central depressant effects on cardiovascular reflexes (27).

During the second postoperative day, a significant inhibition of urinary epinephrine and norepinephrine output by lidocaine was seen. In contrast, no significant effect of lidocaine on urinary levels of dopamine was seen during the second day. This may be explained by the fact that the major part of peripheral dopamine present in plasma and urine probably originates from renal tissue and the splanchnic bed (28) and plays only a minor role in the sympathoadrenal stress response to surgery.

Surprisingly, most of the effects of lidocaine on the

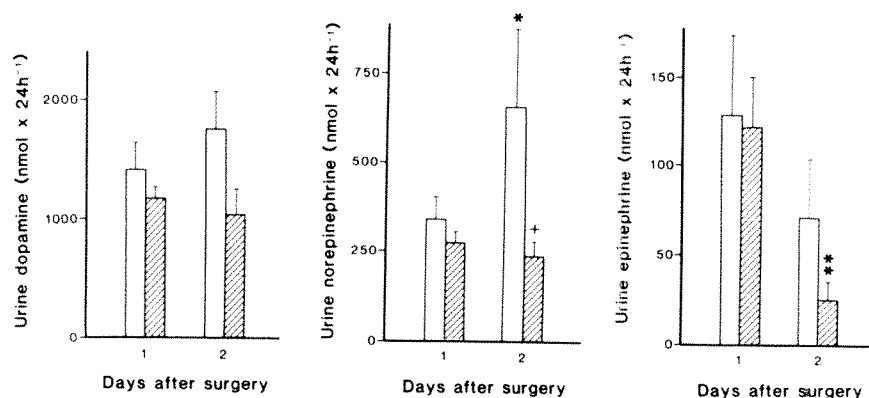


Figure 7. Urinary output of catecholamines during the first and second day after surgery in patients receiving intravenous infusions of lidocaine (shaded bars) compared with control patients (open bars). * $P < 0.05$ compared with control group. ** $P < 0.01$ day 2 vs day 1.

sympathoadrenal response occurred on the second postoperative day, i.e., after the lidocaine infusion was stopped. Such a delayed effect might be related to the extensive damage to the serosal surface associated with abdominal surgery (29) that elicits an inflammatory reaction with release of inflammatory agents including histamine, serotonin, bradykinin, and prostaglandins (30). These agents may act directly on intraabdominal nerve endings of afferent nerve fibers (31,32) and indirectly by sensitization of receptors to stimulation (33, 34). This inflammatory reaction in the area of surgery is probably responsible for the activation and maintenance of reflexes leading to the sympathetic hyperactivity for several days after the mechanical trauma.

Local anesthetics of the amide group have potent antiinflammatory properties related, perhaps, to their structural resemblance to steroid and antihistaminic drugs (35,36). Thus IV infusions of lidocaine at infusion rates similar to ours completely inhibit the inflammatory response to peritonitis in rabbits (37). The antiinflammatory effect of lidocaine is probably mediated through several mechanisms, including inhibition of prostaglandins by disruption of the normal interaction between membranes and prostaglandins (38), inhibition of the migration of leucocytes to the inflammatory area (39,40), inhibition of leucocyte metabolism (41), inhibition of lysosomal enzymes from leucocytes (42), and reduction of vascular permeability in the peritoneum (43). In a recent study, lidocaine was shown to inhibit lymphocyte activity up to 8 days after termination of exposure to lidocaine (44). In addition to this long-lasting antiinflammatory effect of lidocaine, when we consider the fact that the inflammatory reaction to surgery does not begin to become evident until the second postoperative day (45), it becomes reasonable to hypothesize that our results indicate a potent sympatholytic effect of lidocaine during the second postoperative day.

In conclusion, we have shown that continuous IV

infusion of lidocaine for 24 hr during and after elective cholecystectomy effectively suppresses extubation-induced tachycardia and hypertension but does not inhibit the overall sympathetic response during the first day after surgery. However, in addition to an analgetic effect postoperatively, a reduced output of urinary catecholamines occurs during the second postoperative day in lidocaine-treated patients. Because lidocaine infusion is practically devoid of side effects at the present infusion rate, it can be used to increase the rate at which the sympathoadrenal response to major abdominal surgery decreases postoperatively.

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Clinical Reports

Use of a Double-Lumen Endotracheal Tube with Independent Lung Ventilation for Treatment of Refractory Atelectasis

Kenneth J. Bochenek, MD, Morris Brown, MD, and Alvaro Skupin, MD

Clinicians have long been concerned with the management of atelectasis. Numerous techniques have been described to reverse atelectasis in one or more lobes of the lung. The techniques employed have included chest physiotherapy, transnasal tracheal suctioning, translaryngeal instillation of saline or mucolytic agents into the trachea, intermittent positive pressure breathing (IPPB), and bronchoscopy (1). We describe the use of independent ventilation with differential positive end-expiratory pressure (PEEP) for treatment of refractory lobar atelectasis.

Case Report

A 60-yr-old, 50-kg woman came to the emergency room complaining of shortness of breath, severe coughing, generalized weakness, and right upper quadrant pain of several days' duration. The patient's medical history was significant for insulin-dependent diabetes mellitus and a multipack-year history of smoking. On admission, the patient was afebrile, with an arterial blood pressure of 115/70 mm Hg, a pulse of 108 beats/min, and a respiratory rate of 26 per minute. Auscultation of the chest revealed decreased breath sounds with dullness to percussion at the right posterior lung base, accompanied by marked tenderness over the area. The remainder of the physical examination was unremarkable. A chest x-ray film on admission revealed right lower and middle lobe consolidation and pleural thickening with an enlarged azygous node suggestive of a neoplasm. Lung tomograms suggested an infiltrating neoplasm of the

Table 1. Arterial Blood Gas Tensions

	Set number ^a			
	1	2	3	4
FiO ₂	0.21	0.50	1.0	0.45
PaO ₂ (mm Hg)	48	133	114	400
pH	7.22	7.33	7.25	7.47
PaCO ₂ (mm Hg)	70	33	61	36

^aSee text for numbering of samples.

right lung. Bronchoscopy was performed, which revealed undifferentiated oat cell carcinoma with an obstructive lesion of the right upper bronchus and invasion of the bronchus intermedius. There was no evidence of metastatic disease and chemotherapy was initiated while the patient underwent evaluation for radiation therapy.

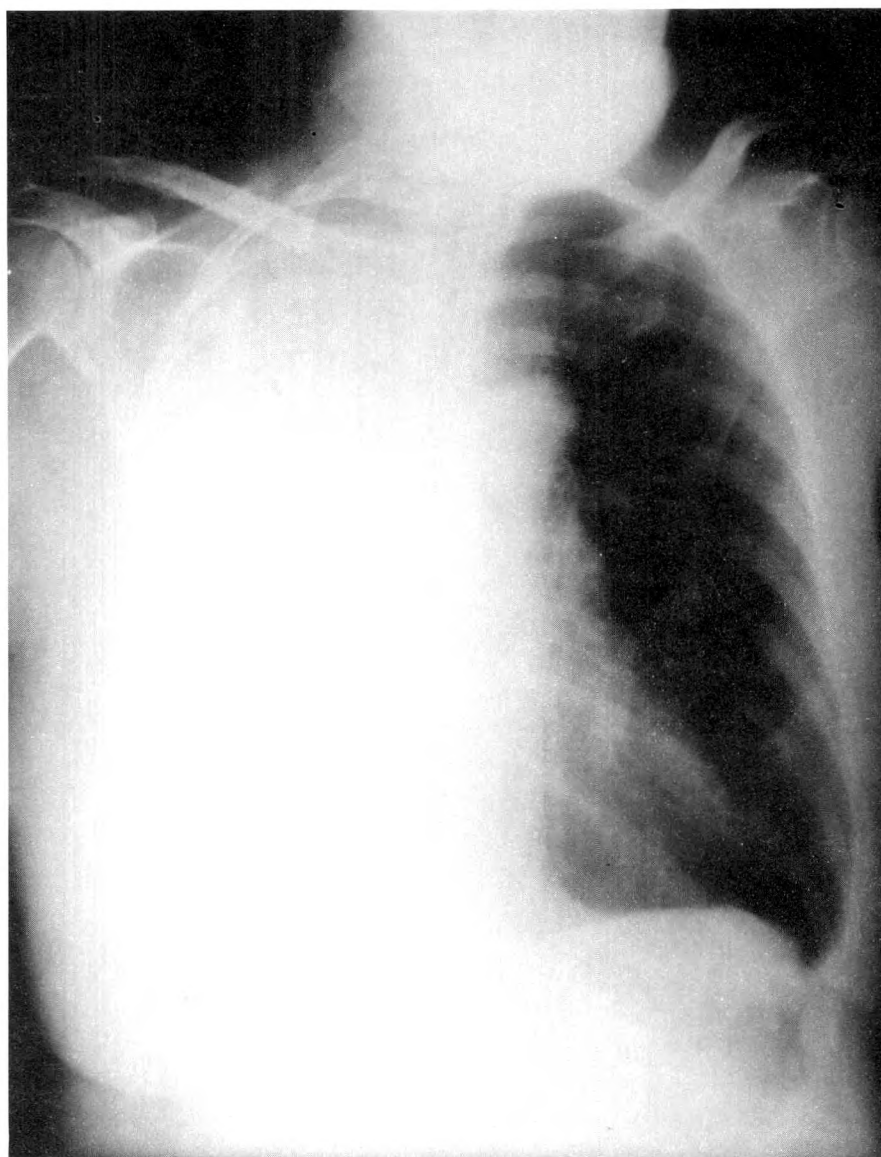
The patient became increasingly dyspneic with arterial blood gas tensions indicating hypercapnia and deteriorating oxygenation (Table 1, set 1), and soon required tracheal intubation with mechanical ventilatory support. Chest x-ray films at that time (Fig. 1), revealed a normal left lung field with complete atelectasis of the right lung. Initial ventilatory settings were: FiO₂ 0.5, tidal volume 600 ml, ventilatory rate 14, and zero end-expiratory pressure (ZEEP). Subsequent arterial blood gas tensions (Table 1, set 2) showed a transient improvement. However, despite chest physiotherapy, tracheal suctioning, fiberoptic bronchoscopy, and low level PEEP therapy, the patient continued to deteriorate. Because of the deterioration in oxygenation despite an FiO₂ of 1.0 and persistent hypercapnea, the patient underwent bronchoscopy with NdYAG laser excision of the tumor.

The postoperative chest roentgenogram revealed complete reexpansion of the right upper lobe with

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Figure 1. Chest roentgenogram obtained immediately after intubation for respiratory failure. Note atelectasis of entire right lung.



persistent atelectasis of the right middle and lower lobes. Despite expansion of the right upper lobe, there was no clinical improvement (Table 1, set 3). Fiberoptic bronchoscopy showed that the previously affected bronchi were still patent. In view of progressive hypoxemia and hypercarbia, independent lung ventilation was instituted using a #37 right Robertshaw endotracheal tube. Synchronized independent ventilation was begun with two MA-1 ventilators (Puritan-Bennett, Overland Park, Kansas) and an intermittent mandatory ventilation (IMV) controller (Healthdyne, Marietta, Georgia). The tidal volume used was 400 ml, with a respiratory rate of 12 per minute, PEEP of 10 cm H₂O on the right and 5 cm H₂O PEEP on the left. The above synchronized settings resulted

in a subsequent improvement in arterial blood gas tensions (Table 1, set 4). Repeat chest x-ray (Fig. 2), showed clearing of the residual atelectasis. Clinically, the patient improved, with a subsequently uneventful replacement of the Robertshaw tube by a single-lumen endotracheal tube after 92 hr of independent lung ventilation. She was extubated 70 hr later and was transferred from the intensive care unit to the general medical floor for continued chemotherapy and radiation therapy.

Discussion

Two principles guide the therapy of established lobar atelectasis: 1) Lung tissue must be expanded by pro-

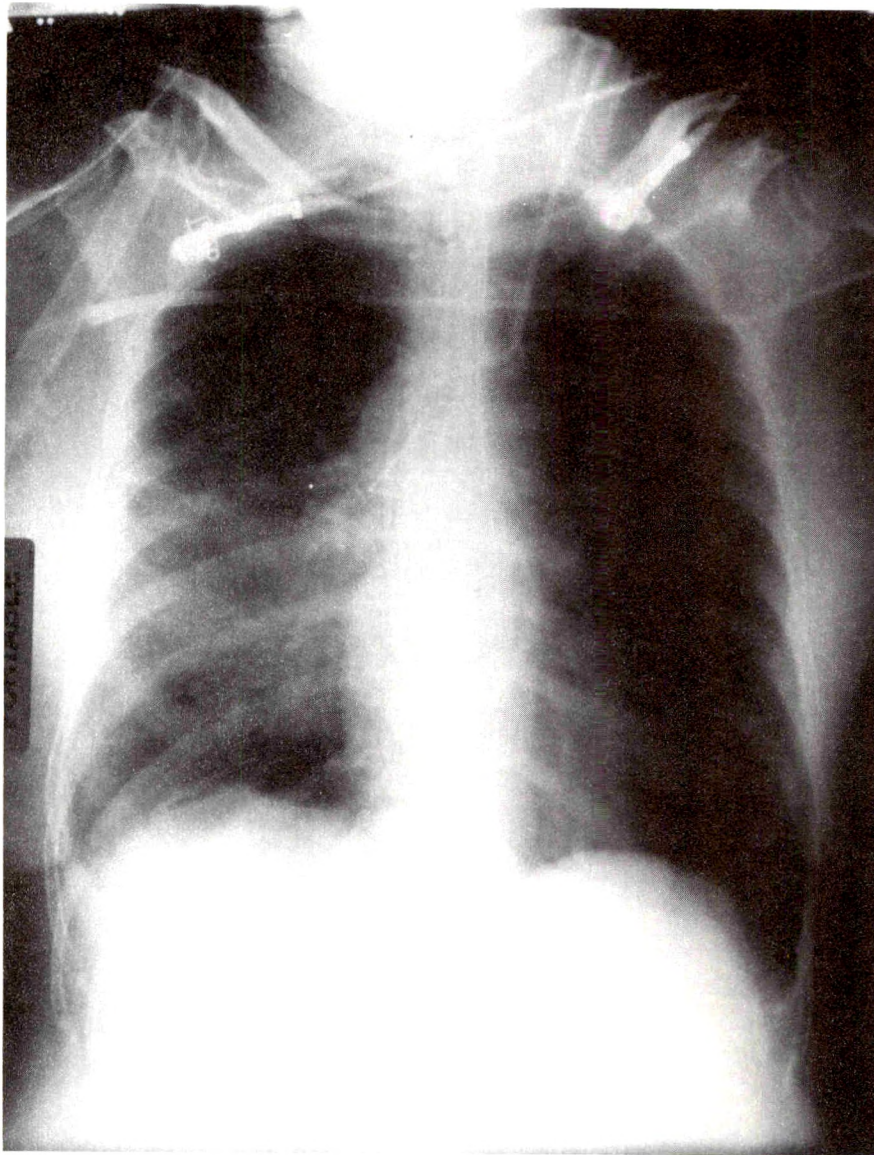


Figure 2. Chest roentgenogram after treatment with the double lumen endotracheal tube and differential PEEP, showing appreciable improvement in right lung atelectasis.

duction of a transpulmonary pressure in collapsed tissue that exceeds the critical opening alveolar pressure, and 2) retained secretions must be removed. Numerous conservative techniques have been described to reverse lobar atelectasis. However, these techniques are directed at removal of secretions and do little in themselves to restore total lung capacity, functional residual capacity, residual volume, or pulmonary compliance. As a result, some patients are not cured by initial attempts to resolve atelectasis (1). Techniques used in these refractory cases include intermittent mask continuous positive airway pressure (CPAP) (2), fiberoptic bronchoscopic balloon dilation (3) with and without saline lavage, tracheal insufflation using a balloon-tipped pulmonary artery catheter (4), and mechanical dilation with bougies (5). In view

of the normal left lung in our patient, this case presented the need to treat unilateral pulmonary disease. Positive end-expiratory pressure is sometimes ineffective in the treatment of unilateral alveolar/airway collapse because the normal lung (with areas of low resistance and high compliance) preferentially receives the elevated pressures while the diseased lung does not benefit.

Isolating the diseased lung from the normal lung is not a new principle. Since their introduction in 1936 by Magill (6), double lumen tubes have gained widespread clinical application. The double-lumen endotracheal tube has been used preoperatively and intraoperatively for many purposes. Isolation of one lung (7) for prevention of spillage or contamination, performance of bronchopulmonary lavage, or control

of ventilation with fistulas are well established uses of the double lumen tube. In addition, surgical exposure is maximized with this tube in thoracic aneurysm repair, pneumonectomy, esophageal resection and lobectomy. The unilateral lung disease in our patient afforded the opportunity to use the double lumen tube for a new indication—refractory atelectasis.

Synchronized independent ventilation was achieved utilizing two MA-1 ventilators (Puritan-Bennett), synchronized with an IMV controller (Healthdyne). Our biomedical technicians produced a system for synchronization by attaching the output of the controller directly to the "manual" switch of each ventilator. An impulse directed from the IMV controller therefore sent a signal simultaneously to both ventilators via the manual circuitry, and synchronized breaths were delivered to the patient. Setting the cycle time on the IMV controller thus resulted in a synchronized firing of the ventilators (e.g., 10 sec = respiratory rate of 6, 5 sec = respiratory rate of 12). As a precaution, a backup respiratory rate lower than the IMV controller is set on each of the ventilators to assure protection against possible failure of the IMV controller.

The ability to provide independent ventilation with

differential PEEP allows compensation for the differences in compliance frequently found in unilateral lung disease. We feel that the double-lumen endotracheal tube offers a valuable alternative for treating unilateral atelectasis when conventional means have failed.

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Comparison of Blood Pressure Measurement by Doppler and by Pulse Oximetry Techniques

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The continuous assessment of arterial oxygen saturation by pulse oximetry was introduced into clinical anesthesia in 1983 (1). Such monitoring has now become standard in our institution for all patients during anesthesia. Routine blood pressure determinations performed in the same extremity with the oximeter probe consistently interrupt the function of the oximeter. Because of this, oximeter probes were usually placed at sites not affected by blood pressure cuff inflation. However, small infants and patients with major burn injuries have little surface area available for multiple sensor placement. In such patients the oximeter probe and the Doppler flow meter for measurement of blood pressure often had to be placed on the same extremity. We noticed that the oximeter pulse display seemed to have some correlation with the systolic blood pressure determined by Doppler methods.

Pulse oximetry functions by placing a pulsating arterial vascular bed between a two-wavelength light source and a detector. It is not known whether the oximeter is as sensitive in detecting arterial pulsation as is a Doppler technique in detecting arterial flow. The use of the pulse oximeter for intraoperative blood pressure measurement has not been reported. This study compares the pulse oximeter with the Doppler technique for measurement of systolic blood pressure.

Methods

The Doppler flow meter used was an Ultrasonic Doppler Flow Detector model 811 with 9.4-MHz probe

from Parks Medical Electronics, Inc. The oximeter was a Pulse Oximeter Model N-100 from Nellcor, Inc. Standard aneroid sphygmomanometers with cuffs appropriate to patient size were employed. The Doppler probe was placed over the radial artery at the wrist and the oximeter sensor was placed on a fingertip of the same arm. Simultaneous paired readings were recorded by a single observer in each patient. Paired *t*-test and analysis of linear regression were used for statistical comparison of the two methods.

Results

Seven hundred twenty-nine pairs of systolic blood pressure readings were obtained in 51 patients. Patients ranged in age from newborn to 79 yr with an average age of 25 yr. Blood pressures ranged from 42 to 205 mm Hg with mean values of 100 mm Hg by oximeter and 103 mm Hg by the Doppler method. The two techniques yielded 272 sets of identical readings. The oximeter reading was higher than the Doppler reading in 109 instances and lower in 348. The relation between the Nellcor Pulse Oximeter readings (*y*) and Doppler technique readings (*x*) was $y = 0.91x + 5.8$ ($r = 0.93$, $P < 0.01$). The mean difference of the paired readings was 4.9 mm Hg with an SD of 7.04.

Eight patients were less than 1 yr old. In 108 pairs of readings from this subgroup the blood pressures ranged from 66 to 120 mm Hg, with mean values of 78 mm Hg with both oximetry and the Doppler method (Fig. 1). Fifty-five sets of readings were identical. The oximeter read higher in 11 instances and lower in 42. The average difference of the paired readings was 2.4 mm Hg with an SD of 4.16.

Six patients were older than 40 yr. In 92 pairs of readings from this subgroup the blood pressures ranged from 60 to 170 mm Hg with mean values of 119 mm Hg by oximetry and 123 mm Hg with the Doppler technique. Thirty-six sets of readings were identical;

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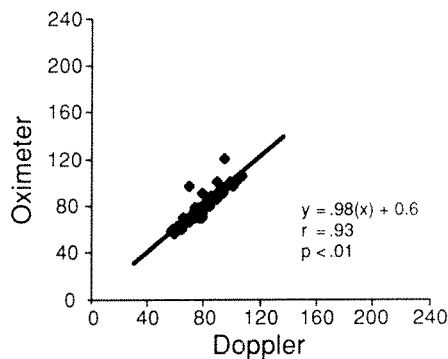


Figure 1. One hundred-eight determinations in eight patients: newborn to 1 yr.

the oximeter reading was higher in 9 instances and lower in 47. The relation between the Nellcor Pulse Oximeter readings and Doppler technique readings was $y = 1.04x - 9.72$ ($r = 0.93$, $P < 0.01$). The average difference of the paired readings was 4.6 mm Hg with an SD of 7.88.

Discussion

Accuracy of blood pressure values varies depending on clinical conditions and the type of direct or indirect method used (2). In this study of 51 patients, systolic blood pressure values determined by pulse oximetry

correlated well with values obtained by a Doppler method ($r = 0.93$). However, the clinical usefulness of this method may apply only to the subgroup of patients less than 1 yr of age. The mean difference between values in this subgroup was 2.4 mm Hg with an SD of 4.16 compared with the overall group, the mean difference of which was 4.9 mm Hg with an SD of 7.04.

When using the pulse oximeter for blood pressure determination, the readings are best taken when the oximeter loses its visual/audible display during blood pressure cuff inflation. Otherwise, the blood pressure cuff must be deflated fairly rapidly to prevent the pulse oximeter from shifting into the "pulse search" mode. This requires practice.

In conclusion, we found the Nellcor Pulse Oximeter to be useful for blood pressure determination, especially in infants and children whose size restricts the space available for noninvasive monitoring devices. Other pulse oximeters may or may not be as useful for blood pressure determination.

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Accidental Epidural Magnesium Sulfate Injection

Alan Dror, MD, and Eva Henriksen, MD

Continuous lumbar epidural infusions of local anesthetics have become increasingly popular (1) as a means of maintaining adequate analgesia during labor with minimal motor blockade when using dilute concentrations of local anesthetics (2,3). Complications are similar to those seen with intermittent injection techniques. Rarely, agents other than local anesthetics have been mistakenly injected into the epidural space. The following case describes the accidental epidural infusion of magnesium sulfate in a parturient.

Case Report

A 26-yr-old gravida 2, para 1 woman was admitted with an intrauterine pregnancy of 40 weeks and early spontaneous labor. She was diagnosed as having mild preeclampsia on the basis of elevated blood pressures, proteinuria, and edema for which an intravenous infusion of magnesium sulfate at 1.5 gm/hr after a 4.0-gm intravenous loading dose, was started. Past medical history was otherwise unremarkable. She had had a cesarean delivery 3 yr earlier under general anesthesia without difficulties. Admission laboratory studies, including serum electrolyte levels, complete blood count, prothrombin time, and plasma fibrinogen levels were within normal limits except for a hematocrit of 32%, which was believed to be consistent with anemia of pregnancy.

An epidural catheter for analgesia during labor was placed easily at the L4-5 interspace by loss of resistance with an 18-gauge Tuohy-Schliff needle and the catheter was advanced 3 cm. Injection of 8 ml 0.5% bupivacaine with epinephrine 1:200,000 resulted in a T-6 level of analgesia to pinprick with complete pain relief. An epidural infusion of 0.125% bupivacaine at a rate of 10 ml/hr was then begun. Three hr later, the epidural catheter tubing was changed because of a malfunctioning pump mechanism. The infusion rate

was increased to 13 ml/hr because the level of analgesia had decreased to T-12 on the right and T-9 on the left. One hr later, the patient still reported right sided pain with contractions. The sensory level of blockade was unchanged. The catheter was withdrawn 1 cm, and the infusion rate increased to 15 ml/hr. One hr later, the patient complained of the sudden onset of bilateral periumbilical continuous burning pain that rapidly worsened. At this time, it was noticed that her magnesium sulfate infusion had been piggybacked into the epidural bupivacaine infusion tubing. The epidural catheter was noted to have migrated out an additional 1 cm and at this point it was removed intact. The level of analgesia and motor blockade had been decreasing gradually and by this time she had no sensory level of analgesia or motor blockade. Her blood pressure was 110/84 mm Hg, pulse rate 80 beats/min, respiratory rate 20 breaths/min, and temperature 37°C. The intense burning worsened during the next 15 min, and then decreased over the next 3 hr, at which time she had no residual dysesthesia or motor blockade. Because labor failed to progress, the patient eventually underwent a cesarean section under general anesthesia. Apgar scores of the female infant were 6 at 1 min, and 9 at 5 min. Six weeks later, the patient was still without paresthesia or motor weakness.

Discussion

Continuous epidural infusions using both local anesthetics and narcotics have been used to maintain desired levels of analgesia and anesthesia. Unfortunately, agents other than those desired have been inadvertently injected into the epidural space. In 1975, Forestner and Raj (4) reported the accidental epidural injection of 15 ml 2% thiopental followed by an injection of a mixture of local anesthetics (bupivacaine 0.25% and lidocaine 0.75% with epinephrine 1:150,000). The patient suffered no neurologic sequelae. Possible factors contributing to this favorable outcome might include dilution of the thiopental with 25 ml epidural saline, epidural vasodilation produced by the local anesthetics (to oppose the thiopental induced vaso-

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constriction), and a decrease in thiopental absorption because of the acidic pH of the local anesthetics. Five percent thiopental was injected in the subarachnoid space of ten patients by Morrison et al. (5) in 1951 in an attempt to evaluate its effect as a spinal anesthetic. One patient developed transient hypesthesia over the right leg for 5 weeks. There were no other apparent complications, suggesting that spinal thiopental is relatively benign neurologically.

Potassium chloride (KCl) has also been injected accidentally into the epidural space in strengths of 0.2 (6) to 11.25% (7), with pain being the usual clinical manifestation. When administered in strengths up to 6.43% (8), recovery was complete. The patient who received 11.25% KCl developed a T-7 paraplegia that persisted until death 6 months later.

Recently, Lin et al. (6) described a case of accidental epidural injection of 0.2% KCl and 2 mg diazepam, resulting in lower extremity pain and a T-10 sensory and motor block. An attempt to dilute the KCl by epidural injection of saline had the potentially harmful effect of spreading both the level of anesthesia and the KCl-diazepam mixture. The pain, as well as the sensory and motor block, resolved completely after 5.5 hr.

Magnesium sulfate has been the long-standing anticonvulsant of choice for treating the pre-eclamptic or eclamptic patient, although, at higher doses, it is also used as a tocolytic (9). It is usually given as a 4.0-gm IV loading dose, followed by 1.0–2.0 gm/hr. Magnesium decreases acetylcholine release from the presynaptic motor neuron, decreases motor end plate sensitivity to acetylcholine, and decreases muscle membrane excitability. It does not cross the blood brain barrier, but does create a flaccid weakened state.

In the present case, a 10% solution of magnesium sulfate was accidentally piggybacked into the continuous bupivacaine infusion tubing. The solution of magnesium sulfate, prepared in sterile water without preservatives with a pH of 7.39, had an osmolarity of approximately 425 milliosmoles/L. This error could have occurred any time after the tubing was changed because of the pump failure. Since the magnesium sulfate infusion was set at 10 ml/hr (1.5 gm/hr), the patient could have received a maximum of 3 gm in the epidural space. The epidural catheter used has three ports located 0.5, 1.1, and 1.5 cm from the tip. At the time of removal of the catheter, it was noted that probably only 1 cm of the catheter was still in the epidural space. Therefore, if equal amounts of fluid going through the epidural catheter exited each hole, only one-third of the injectate would have been injected into the epidural space (through the third distal port). Thus, it is not surprising that the patient

did not have a sensory block and still had labor pain. Also, even small amounts of magnesium sulfate in the epidural space can be very irritating.

Several interventions have been proposed to decrease the toxicity of accidental epidural injections, including introducing a second epidural catheter at a higher interspace and lavaging with saline (4), and dilution of the injectate with saline (6), steroids (4), or local anesthetics (4). In this case, an undetermined amount of magnesium sulfate (perhaps < 1 gm) entered the epidural space, causing transient intense periumbilical burning pain. None of the above interventions were undertaken and the patient had complete resolution of her pain without adverse neurologic sequelae. Because of this episode, tape is now securely wrapped around all injection ports on the tubing used for continuous epidural infusions in our institution, and personal communication is emphasized between house officers and nursing personnel to minimize the risk of repetition of the situation described here. Other possible steps include use of tubing without extraneous ports (10), color-coding the tubing (11), or adding water-soluble dye to the injectate. As epidural catheters and continuous infusions increase in popularity, vigilance remains essential to minimizing the risk of having inappropriate drugs mistakenly injected into the epidural space.

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Topical Nitroglycerin for Intraoperative Penile Turgescence

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Intraoperative penile turgescence, although not a common problem, can render cystoscopy and other urological procedures difficult, if not impossible. A number of treatments have been suggested, the most recent being the use of ketamine (1-5). However, the use of ketamine is not benign and occasionally results in undesirable side effects: cardiovascular changes consisting of increases in blood pressure and cardiac output are not uncommon with the use of ketamine. Moreover, there is up to a 15% incidence of hallucinations, which is of special concern in a group of patients that is usually awake under regional anesthesia.

The following is a case report of the use of topical nitroglycerin as a new method for treatment of this intraoperative complication, followed by a discussion of the pertinent pharmacology and physiology.

Case Report

A 55-yr-old male patient with a history of urinary retention considered secondary to benign prostatic hypertrophy was scheduled for a transurethral resection of the prostate. The patient's only other reported medical problems were previous bladder calculi. He was being treated with no medications and had no allergies. He was designated ASA Class I.

The patient came to the operating room having received no preoperative medications and was given small doses of diazepam IV, up to a total of 10 mg. A spinal anesthetic was performed using 10 mg 1% tetracaine in an equal volume of 10% dextrose; a sensory level of T6-8 was achieved. The patient was placed in a lithotomy position, surgically prepared and draped and, 20 min after the spinal was performed, the cystoscope was inserted. One hr after starting the spinal anesthesia and 40 min after surgery was started, penile turgescence occurred, rendering continuation of

the procedure impossible. There was no indication of inadequate anesthesia. In an attempt to correct the situation, the patient was given a bolus of 25 mg nitroglycerin (NTG) IV. After about 60 to 90 sec, the NTG had a partial effect for about 1 min, after which time the penile turgescence recurred. A second dose of NTG (50 mg) IV was given, again with partial benefit for about 1 min with recurrence of turgidity. A third dose of NTG (75 mg) had similar results. During this time, the patient's blood pressure, which had been 120-140/70-80 mm Hg before the spinal, transiently decreased from 140/80 to about 110/60 mm Hg. As surgery could not continue with the erection present, it was felt that topically applied NTG paste might be effective. One and one-half inches of 2% NTG paste was applied to the shaft of the penis with complete detumescence occurring within minutes. Surgery was completed without further recurrence. In the operating room, the blood pressure decreased from 140/80 to 120/70 mm Hg after application of the NTG paste. However, 1 hr after the application, and with the patient in the recovery room, the blood pressure decreased to 90/60 mm Hg. This decrease in blood pressure was not associated with any mental alterations, and the low pressure responded promptly to increased fluids and use of the Trendelenburg position.

Discussion

The successful use of inhaled amyl nitrate for the treatment of acute intraoperative penile tumescence was reported by Welti and Brodsky in 1980 (6). They postulated that the occurrence of penile detumescence with amyl nitrate during general anesthesia might be explained by relaxation of the corpora cavernosa venous drainage sites, while the compensatory reflex sympathetic discharge provoked by the rapid blood pressure decrease may mimic the sympathetic discharge that occurs during orgasm, which precipitates arteriolar constriction and termination of erection. However, there are important drawbacks to the use of amyl nitrate. First, amyl nitrate can have a profound hypotensive effect when used in association with regional anesthesia; and second, amyl nitrate

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vapor forms a potentially explosive mixture in oxygen and air, especially hazardous when used in association with cautery.

Nitroglycerin is a dilator of both arterial and venous smooth muscle, but in low concentrations nitroglycerin produces dilation of the veins that predominates over that of arteries (7). Additionally, topical application of nitroglycerin ointment is well absorbed through the skin and allows a sustained effect. It is possible that applying the nitroglycerin ointment to the penis would augment its vasodilating effect on the vasculature of the engorged penis.

The mechanism for the initiation and subsequent subsidence of penile erection is controversial. Erection is mediated by parasympathetic innervation passing from the sacral portion of the spinal cord. Engorgement of the corpora cavernosa, the major event in penile turgescence, is probably regulated by a series of shunts in the penile arterial tree, which act to direct blood toward or away from the cavernous tissue, thereby increasing or decreasing, respectively, the state of penile turgescence (8).

Whether nitroglycerin would primarily vasodilate the venous outflow tract or act at these shunts is not

known. However, if further testing of nitroglycerin for intraoperative penile turgescence continues to show a beneficial effect, perhaps additional knowledge in this area of physiology could be gained, as well as a new treatment for a difficult intraoperative problem.

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Thiopental Dose-Response Relations in Unpremedicated Infants, Children, and Adults

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Little is known about the dose-response relation for thiopental induction of anesthesia in either infants or children. Smith (1) claims that a thiopental dose of 4 mg/kg "is suitable to induce sleep" in pediatric patients, whereas Swedlow (2) recommends 4–6 mg/kg. Coté et al., who determined the dose-response relation for thiopental for children 5–15 yr of age, "recommend that unpremedicated, healthy children receive 5–6 mg/kg intravenous thiopental so that most are sedated adequately" (3). Although they did not obtain comparable data in adults, they concluded that dose requirements were greater in older children than in adults. No studies of the dose-response relation for thiopental have been performed in infants or children <5 yr of age. Thus, the dose-response relationship for thiopental was determined in infants, young children, and adults and results were compared to those of Coté et al. (3).

Methods

Following approval from our Committee on Human Research and Informed Consent, we studied 26 infants (1–11 months), 24 young children (1–4 yr), and 25 adults (18–42 yr). All patients were ASA Class I or II. Patients were not premedicated and had no history of chronic intake of sedatives, in particular, barbiturates. In infants and children, thiopental was injected as an IV bolus over 5 sec into a 25-g butterfly needle or a preexisting IV catheter in an upper extremity, followed by 5 ml of saline. Adults were given thiopental as a bolus into an IV catheter through which saline was being administered rapidly. Patients received one of five doses of freshly-prepared thiopental

(Pentothal, Abbott Pharmaceuticals): 2.0, 2.7, 3.7, 5.1, or 7.0 mg/kg body weight. This range of doses was selected on the basis of a preliminary study, the results of which are not included in the present study; the doses are spaced logarithmically.

At predetermined intervals (30, 45, and 60 sec for infants and young children; 30, 60, and 90 sec for adults), lid reflex, corneal reflex, and trapezius reflex were assessed. Facemask reflex was determined in infants and young children at the same time intervals. Reflexes were assessed earlier in infants and young children because preliminary observation suggested that peak effects occurred earlier in these patients than in adults.

Lid reflex was evaluated by stroking the eyelashes with a cotton swab and observing for movement of the lid. Corneal reflex was evaluated by touching the cornea with a cotton swab and observing for blinking. Trapezius reflex was evaluated by firmly squeezing the trapezius muscle and observing for movement of the extremities, eye opening, or vocalization. Face-mask reflex was evaluated by placing an anesthesia mask over the patient's mouth and nose and observing for grimacing, withdrawal, or crying; this reflex was not assessed in adults or in pediatric patients who did not respond to the mask before receiving thiopental. With all reflexes, responses were graded as either present or absent. Because of the variability in onset and duration of the response to thiopental, analyses were performed using the maximum response, i.e., a reflex was described as absent if it could not be elicited at any one of the three evaluations. Doses were selected randomly by one investigator on the basis of the patient's hospital number. All reflexes were assessed by the other investigator, who was unaware of the thiopental dose.

For each reflex, dose-response curves were analyzed using log-probit analysis (4) to determine ED₅₀ (the dose that produces loss of the reflex in 50% of the patients), and its 95% confidence limits. We also determined ED₉₀.

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Table 1. Incidence of Loss of Reflexes^a

	Dose (mg/kg)				
	2.0	2.7	3.7	5.1	7.0
Infants					
Lid reflex	0/6	1/5	3/5	3/5	5/5
Corneal reflex	0/6	0/5	2/5	3/5	5/5
Trapezius reflex	0/6	0/5	0/5	0/5	0/5
Facemask reflex	1/5	1/5	2/4	2/5	5/5
Young children					
Lid reflex	0/3	0/5	3/5	4/5	6/6
Corneal reflex	0/3	0/5	1/5	4/5	5/6
Trapezius reflex	0/3	0/5	0/5	0/5	0/6
Facemask reflex	0/3	1/4	1/4	5/5	5/5
Adults					
Lid reflex	0/5	0/5	2/5	3/5	5/5
Corneal reflex	0/5	0/5	3/5	3/5	5/5
Trapezius reflex	2/5	2/5	5/5	5/5	5/5

^aNumber losing reflex/number of patients studied.Table 2. ED₅₀, 95% Confidence Limits for ED₅₀, and ED₉₀ for Loss of Each Reflex (mg/kg)

	ED ₅₀	95% confidence limits for ED ₅₀	ED ₉₀
Lid reflex			
Infants	3.9	2.8-5.5	6.4
Young children	3.7	3.0-4.7	5.3
Adults	4.2	3.3-5.4	6.0
Corneal reflex			
Infants	4.4	3.2-6.1	7.0
Young children	4.7	3.6-6.1	6.9
Adults	4.1	3.1-5.4	6.1
Trapezius reflex			
Infants	>7.0	"	"
Young children	>7.0	"	"
Adults	<3.7	"	"
Facemask reflex			
Infants	4.1	2.8-5.9	8.6
Young children	3.4	2.5-4.7	4.6

"Could not be determined; see text for explanation.

Results

The incidence of loss of the various reflexes we tested is shown in Table 1. Dose-response curves for lid, corneal, and facemask reflex for the different age groups did not differ from parallelism. Values for ED₅₀ for lid and corneal reflexes were similar in infants, young children, and adults (Table 2). The ED₅₀ for facemask reflex was similar for infants and young children; this reflex was not assessed in adults. None of the infants or young children lost the trapezius reflex with doses as large as 7.0 mg/kg, whereas 19 of 25 adults lost this reflex. Because the responses of infants, young children, and adults to the trapezius reflex were not uniformly distributed over the range of doses, we were unable to calculate values for ED₅₀, its confidence limits, and ED₉₀.

Discussion

The maturational changes that occur during infancy result in differences in the pharmacokinetic or pharmacodynamic characteristics, or both, of several drugs administered during anesthesia, e.g., *d*-tubocurarine (5), vecuronium (6), neostigmine (7), and edrophonium (8). We expected that these maturational changes might produce differences among infants, children, and adults in their responses to thiopental. In fact, the dose of thiopental required for the loss of the trapezius reflex is markedly greater in infants and young children than in adults. However, the dose of thiopental required for loss of lid, corneal, and facemask reflexes did not change with age.

There are several factors, both pharmacokinetic and pharmacodynamic, that might influence the response

to thiopental. The first of these is the peak concentration of thiopental in the brain. Because thiopental is highly lipid-soluble, it crosses the blood-brain barrier rapidly, and the peak concentration in the brain is a function of the peak concentration in the blood and permeability of the blood-brain barrier. In turn, the peak concentration in the blood is a function of the volume of the central compartment (V_1). Sorbo et al. (9), who determined the pharmacokinetics of thiopental in two infants and 14 children, reported that V_1 for thiopental was similar for pediatric patients (0.4 ± 0.19 L/kg, mean $\pm$ SD) and adults (0.28 ± 0.11 L/kg). However, they obtained venous blood samples from pediatric patients and compared their results to values in adults from whom arterial blood samples had been obtained. Homer and Stanski (10) reported that the concentration of thiopental differs between arterial and venous blood; consequently, values for V_1 obtained using venous samples will differ from those obtained using arterial samples. As a result, the values for V_1 reported by Sorbo et al. (9) are probably not comparable to those obtained in adults. There are no other data regarding pharmacokinetics of thiopental in pediatric patients.

The second factor that may influence the response to thiopental is the extent of protein binding, because only the unbound fraction can cross the blood-brain barrier. Sorbo et al. (9) demonstrated that the free fraction of thiopental was similar in pediatric patients ($13.2 \pm 1.5\%$) and adults ($13.6 \pm 1.3\%$). Thus, the extent of protein binding is unlikely to influence the response to thiopental. The remaining factor, age-related differences in the responsiveness of the brain

to thiopental, has not been investigated. Thus, we are unable to use known physiologic differences between pediatric patients and adults to predict age-related differences in the response to thiopental.

We found that the dose required to depress one reflex, the trapezius reflex, changes with age, whereas the dose required to depress the other reflexes we tested does not. If the age-related differences for the trapezius reflex were the result of age-related changes in pharmacokinetics, we would expect (but did not find) similar age-related differences for the remaining reflexes. This suggests that the difference between the trapezius reflex and the other reflexes we tested is pharmacodynamic. The stimulus used to elicit the trapezius reflex is painful, in contrast to the stimuli used to elicit the other reflexes. Our findings suggest that the dose of thiopental required to block a painful reflex decreases with age.

Although we did not study older children, a comparable study was performed by Coté et al. (3) in 54 children aged 5–15 yr. They evaluated the same reflexes as in our study, with one difference—they assessed the facemask reflex by placing the facemask, moving the chin to the “sniffing position”, and beginning assisted ventilation. Despite this difference, we believe that the data obtained in the two studies are comparable. The values they obtained for facemask reflex (ED_{50} 3.4 mg/kg; range 2.7–4.3) and for corneal reflex (ED_{50} 4.8 mg/kg; range 3.6–6.4) are similar to those we obtained in both younger and older subjects. Their values for lid reflex (ED_{50} 2.9 mg/kg; range 2.3–3.7) are lower than those obtained in the present study. Their values for trapezius reflex (ED_{50} 5.0 mg/kg; range 3.7–6.7) are intermediate to those values we obtained in younger patients (infants and young children) and in older subjects (adults). Thus, the findings of Coté et al. are consistent with our findings that there are no age-related changes in dose requirements for ablation of the corneal and facemask reflex, and that dose requirements for the ablation of the trapezius reflex decrease with age.

The results of the present study differ from those obtained by Becker (11). He administered thiopental by continuous infusion to adults undergoing surgical procedures and measured the plasma concentration of thiopental at the time that eyelid reflex, corneal reflex, and trapezius muscle reflex disappeared. In study subjects who received only thiopental, plasma concentrations of thiopental were similar at the time that trapezius reflex and corneal reflex disappeared (42 ± 3 and 39 ± 2 μ g/ml, respectively). These values exceeded the plasma concentration at the time that eyelid reflex disappeared (26 ± 2 μ g/ml). Although Becker measured plasma concentrations rather than

the dose that resulted in loss of these reflexes, his results suggest that, in adults, similar doses may be required to depress the trapezius muscle and corneal reflexes, and that smaller doses may be required to depress the eyelid reflex. We are unable to explain the discrepancy between his results and our findings in adults.

Thiopental is usually administered to achieve one of two primary goals: to provide a smooth transition to an inhalational anesthetic, or to permit laryngoscopy and tracheal intubation. To accomplish the former, thiopental should produce obtundation and, possibly, loss of consciousness. Whether thiopental has produced a state of obtundation or unconsciousness is reasonably assessed using the facemask, lid, or corneal reflexes. The results of our study suggest that the dose of thiopental required to permit transition to an inhalational anesthetic is probably similar for pediatric patients and adults. Testing for a response to a facemask is primarily useful in the pediatric age group; absence of this reflex would suggest conditions suitable for the induction of a deeper plane of anesthesia with an inhalation anesthetic. Therefore, the ED_{50} (or ED_{90}) for loss of this reflex is probably the most meaningful dose to use in determining the dose of thiopental for the induction of anesthesia in infants and children.

In contrast, if thiopental is used as the sole anesthetic agent for tracheal intubation, which is probably more stimulating than either skin incision (12) or stimulation of the lid or cornea, the dose required is probably represented by the dose needed to block the trapezius response. Consequently, if thiopental is the only anesthetic drug administered before laryngoscopy and tracheal intubation, dose requirements are probably larger in pediatric patients than in adults.

In summary, the dose of thiopental required to produce loss of the lid and corneal reflexes is similar in pediatric patients and adults. As a result, if thiopental is used to produce unconsciousness (as assessed by these reflexes), similar mg/kg doses should be administered to pediatric patients and adults. The dose of thiopental required to produce loss of the trapezius reflex is larger in pediatric patients than in adults. If the trapezius reflex is considered analogous to the stimulus of laryngoscopy and tracheal intubation, then the dose of thiopental required to prevent a response to these stimuli is larger in pediatric patients than in adults.

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Hemodynamic and Metabolic Effects of Two Anesthetic Techniques in Children Undergoing Surgical Repair of Acyanotic Congenital Heart Disease

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Few comparative data are available to indicate whether fentanyl or isoflurane is better for use in children undergoing operative repair of acyanotic congenital heart disease. In addition, the catecholamine responses in children with congenital heart disease before cardiopulmonary bypass have not been described with either technique. The purpose of our study was to compare the hemodynamic and catecholamine responses to anesthesia and surgical stimulation with isoflurane to those with a fentanyl/diazepam combination in the pre-bypass period, in children undergoing surgical repair of acyanotic congenital heart disease.

Methods and Materials

After Institutional Review Board approval of the study and parental informed consent were obtained, 27 children in ASA category II with acyanotic congenital heart disease (either atrial [ASD] or ventricular [VSD] septal defect) were enrolled. All were sedated with either rectal (22 mg/kg) or intravenous (2-3 mg/kg) thiamylal. Arterial and central venous catheters were placed percutaneously; thereafter, arterial pressure (systolic, diastolic and mean [MAP]), central venous pressure (CVP) and electrocardiogram (ECG) were monitored continuously. End-tidal (ET) concentrations of carbon dioxide (CO₂) and isoflurane (I) were monitored by mass spectrometry.

All children were randomly assigned to one of two groups. Patients in group I ($n = 15$) received isoflurane, initially to 1.5 MAC ET (MAC estimates adjusted

for age [1]), then adjusted as necessary to maintain MAP within 20% of control values. Patients in group II ($n = 12$) received fentanyl 75 μ g/kg and diazepam 0.4 mg/kg IV. One-half of the fentanyl and all of the diazepam were given before tracheal intubation, and the remaining fentanyl was given between intubation and skin incision. All patients received pancuronium 0.1 mg/kg during induction and again before cardiopulmonary bypass (CPB). All patients received 100% oxygen throughout the study (except for those given 1-3% isoflurane in group I).

Baseline data obtained before induction included heart rate (HR), MAP, CVP, arterial pH, arterial oxygen (PaO₂) and carbon dioxide (PaCO₂) tension, ET CO₂, ET isoflurane, and arterial epinephrine and norepinephrine levels. Arterial samples for measurement of catecholamine levels were placed in sodium bisulfite-containing tubes, centrifuged, and frozen until assayed. Catecholamines were extracted from plasma fractions using alumina and were measured using high performance liquid chromatography.

Additional measurements were made 1) after induction and before intubation, 2) 2 min after intubation, 3) 2 min after incision and 4) 2 min after initiation of CPB. Student's *t*-test for unpaired data was used to compare group I to group II data for each collection time. Within groups, analysis of variance

Table 1.

	Group I (isoflurane) ($n = 15$)	Group II (fentanyl) ($n = 12$)
Males	5	3
Females	10	9
Age (yr: mean $\pm$ SD)	6.2 $\pm$ 4.9	4.8 $\pm$ 3.8
Weight (kg: mean $\pm$ SD)	26.4 $\pm$ 18.2	22.6 $\pm$ 18.9
Congenital defect		
ASD	11	5
VSD	4	7

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Table 2.

		Baseline	Induction	Intubation	Incision	CPB
End-tidal isoflurane (%)	Group I	—	1.5 ± 0.3	1.4 ± 0.3	1.5 ± 0.4	0.9 ± 0.0
	Group II	—	—	—	—	—
Heart Rate (beats/min)	Group I	102 ± 12	129 ± 2 ^{a,c}	142 ± 18 ^{a,d}	134 ± 11 ^{a,d}	—
	Group II	102 ± 17	100 ± 12	99 ± 13	94 ± 14	—
MAP (mm Hg)	Group I	73 ± 9	73 ± 4	80 ± 15	74 ± 12	54 ± 10 ^a
	Group II	78 ± 2	76 ± 10	75 ± 11	85 ± 13	45 ± 11 ^a
CVP (mm Hg)	Group I	7 ± 3	7 ± 3	7 ± 3	8 ± 2	8 ± 3
	Group II	6 ± 3	8 ± 3	8 ± 3	8 ± 3	8 ± 4
Epinephrine (pg/ml)	Group I (n = 5)	18 ± 36	22 ± 32	48 ± 54	140 ± 141	725 ± 341 ^a
	Group II (n = 7)	389 ± 415	156 ± 251	159 ± 259	78 ± 149	213 ± 340
Norepinephrine (pg/ml)	Group I (n = 5)	184 ± 122	113 ± 71	144 ± 92	134 ± 83	150 ± 69
	Group II (n = 7)	200 ± 118	153 ± 119	131 ± 109	199 ± 177	337 ± 220
PaO ₂ (mm Hg)	Group I	140 ± 83	431 ± 131 ^a	414 ± 116 ^a	460 ± 74 ^a	363 ± 106 ^a
	Group II	112 ± 28	442 ± 92 ^a	413 ± 50 ^a	452 ± 74 ^a	315 ± 120 ^a
pH	Group I	7.36 ± .03	7.40 ± .07	7.41 ± .07	7.54 ± .07 ^a	7.46 ± .08
	Group II	7.35 ± .03	7.35 ± .06	7.38 ± .07	7.51 ± .06 ^a	7.38 ± .06
PaCO ₂ (mm Hg)	Group I	41 ± 4	39 ± 5	36 ± 8	23 ± 5 ^a	27 ± 5 ^{a,b}
	Group II	43 ± 5	41 ± 7	37 ± 8	26 ± 4 ^a	35 ± 9
Time after induction (min)	Group I	—	—	—	—	82 ± 13
	Group II	—	—	—	—	86 ± 18

All values are mean ± SD.

^aP < 0.05 compared to baseline.^bP < 0.05 compared to Group II.^cP < 0.01 compared to Group II.^dP < 0.005 compared to Group II.

was used to compare control with subsequent values. Statistical significance was defined for values with $P < 0.05$.

Results

There was no statistical difference in the demographic data between the patients in the two groups (Table 1). The cardiopulmonary and catecholamine data are summarized in Table 2. Heart rate increased significantly above baseline levels with isoflurane after induction and remained elevated after intubation and incision. In the patients given fentanyl/diazepam, heart rate remained unchanged throughout the study period. Mean arterial pressure remained unchanged from baseline levels at each study period for both groups; however, for all patients in group I, induction with 1.5-MAC isoflurane resulted in a > 20% decrease in MAP, requiring a decrease in mean inspired isoflurane concentration to < 1 MAC to restore MAP to baseline levels. No significant changes in CVP occurred in either group.

Catecholamine levels were stable throughout the study period in group II; in group I, epinephrine levels increased significantly 2 min after the initiation of

cardiopulmonary bypass, at which time mean ET isoflurane concentration was 0.9%.

Discussion

In this study, fentanyl, 75 µg/kg with diazepam, 0.4 mg/kg caused no significant alteration in MAP, HR, or CVP before cardiopulmonary bypass in children with acyanotic congenital heart disease. By contrast, isoflurane 1.5 MAC resulted in > 20% reduction in MAP. By reducing inspired isoflurane concentration to 0.75–1.0 MAC, MAP could be maintained at baseline levels, but HR increased above baseline levels. This increase in HR was not associated with alterations in serum catecholamine levels during the prebypass period and may have resulted from baroreceptor reflexes secondary to systemic vasodilation. The two anesthetic techniques may not be equipotent, which may also account for the hemodynamic differences. Epinephrine levels in patients given isoflurane increased significantly after initiation of CPB, whereas catecholamine levels were stable throughout the study in patients given fentanyl/diazepam.

The hemodynamic stability seen with the combination of 75 µg/kg fentanyl and 0.4 mg/kg diazepam

was superior to that reported with 50–75 $\mu\text{g/kg}$ fentanyl alone (2) or with 30 $\mu\text{g/kg}$ fentanyl with or without 50% nitrous oxide (3). A decrease in systemic arterial pressure and an increase in heart rate during isoflurane anesthesia have been previously reported, both in ASA category I children (4–6) and in children with congenital heart disease (7). The use of pancuronium 0.1 mg/kg for muscle relaxation in our patients may have contributed to the increase in heart rate (8,9). Inadequate anesthesia seems an unlikely cause because catecholamine levels did not change.

Either of the two anesthetic techniques investigated in this study can be administered safely to most children with congenital heart disease. The tendency for isoflurane to cause hypotension and tachycardia may make it less desirable for use in children in whom maximal hemodynamic stability is desirable. In addition, isoflurane, if used, should be continued or supplemented with intravenous agents at the initiation of CPB to attenuate or prevent a stress response.

In summary, the hemodynamic and catecholamine response to induction of anesthesia and surgical stimulation was studied in children with acyanotic congenital heart disease given either isoflurane (1.5 MAC) or fentanyl (75 $\mu\text{g/kg}$)/diazepam (0.4 mg/kg). The patients given isoflurane demonstrated significant increases in heart rate and decreases in blood pressure; a significant rise in epinephrine levels occurred after initiation of CPB. The patients given fentanyl/diaze-

pam had no change from baseline heart rate, blood pressure, or catecholamine levels. The different response to the two techniques may be explained in part by a difference in anesthetic potency.

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Alternating Periodic Leg Movement Induced by Spinal Anesthesia in an Elderly Male

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Alternating periodic movements of the lower leg were observed in an elderly male patient during spinal anesthesia on two separate occasions. The same movements were observed during sleep. There is no previous report of alternating periodic leg movement induced by spinal anesthesia in a patient with sleep-related (nocturnal) myoclonus (1). This is a report of the clinical picture and an hypothetical explanation.

Case Report

Our patient was an 81-yr-old man weighing 59 kg with a height of 150 cm and was brought to the operating room for bilateral ureterostomy. During the past several years he had had repeated transurethral resections of a bladder tumor under saddle blocks. Whether abnormal movements of the legs took place during these operations was not known. Otherwise he was found to be in good general health. His pulse rate was 72 beats/min, blood pressure 130/70 mm Hg, and percent vital capacity 100.3. He was neither a smoker nor a drinker.

Premedication consisted of hydroxydione, 50 mg and atropine sulphate, 0.5 mg. Both were given IM. He was placed in the right lateral decubitus position and lumbar puncture was performed at the L3-4 interspace with free flow of clear cerebrospinal fluid. Dibucaine, 3.6 mg diluted with 1.2 ml 5% saline, an isobaric solution, was injected into the subarachnoid

space. The patient was then turned to the supine horizontal position. Three to four minutes later, we observed left knee and plantar flexion. Within 3 min, the level of analgesia to pinprick reached T-8, making the surgery at the dermatome T-10 to T-12 possible. Three to four minutes later, flexion of the left knee disappeared but the left plantar flexion persisted (i.e., consecutive stereotyped cogwheel slow movement), each lasting 3-4 sec and occurring at intervals of 20-23 sec. He was able to respond to verbal command. During this period blood pressure was 120/60 mm Hg. The respiratory excursion was smooth and regular. Left plantar flexion continued for approximately 70 min before spontaneously subsiding. Surgery continued for 2.5 hr. By the end of the third hour, the level of analgesia had regressed to T-10. There was no movement of the right leg.

The patient's wife, when informed of this episode, said he had similar movements of the lower extremities when asleep at night. This suggested to us the possibility that he suffered from sleep-related myoclonus. The patient consented to polysomnography (sleep study), which was performed 5 weeks after the surgery. Two hours after he fell asleep, electrical activity of the bilateral anterior tibialis muscles was observed on polygraphic tracings. This activity, lasting 3-4 sec and occurring every 20-23 sec, was associated with leg movement, that was directly observed and recorded on videotape. The movement appeared to be the same as that seen during spinal anesthesia. Electroencephalogram and electro-oculogram suggested the stage of sleep during this episode was one to three including non-REM. No myographic activity was noted during REM.

The second episode occurred when the patient returned for total urinary cystectomy 3 weeks after the sleep study. To avoid the effect of premedicants on the level of consciousness, no premedication was given. For intraoperative monitoring unrelated to his unusual response to spinal anesthesia, a catheter was in-

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roduced into the trachea through the cricothyroid membrane for measurement of end-tidal CO_2 and 25-gauge Teflon catheters were placed in both the left radial and the left dorsal pedal artery for blood sampling and monitoring of arterial pressure. Epidural puncture was performed in the left lateral decubitus position. An epidural catheter was introduced at L2-3 so that epidural anesthesia could be administered in case surgery was prolonged. A lumbar puncture was then performed and dibucaine, 3.6 mg diluted with 1.2 ml 5% saline (as in the previous anesthetic) was injected intrathecally at L3-4. The patient was turned to the supine position. This time right knee and plantar flexion-extension took place followed by onset of left knee and plantar flexion. After 3-4 min, only bilateral plantar flexion persisted. The patient was fully awake and his respiratory pattern was unaltered; PaCO_2 was normal. The level of analgesia to pinprick was T-6. The operation lasted for a total of 6.5 hr. Epidural anesthesia with 0.5% bupivacaine was instituted for the latter half of this period. Bilateral plantar flexion continued for 80 min and then disappeared.

Discussion

According to the diagnostic criteria of The Association of Sleep Disorder Center (1), the movement that occurred while this patient slept was sleep-related myoclonus. Because the pattern and the duration of movement as well as the interval between movements were exactly the same as those seen in sleep-related myoclonus, we concluded that the unusual response of the patient to spinal anesthesia may be a related phenomenon. There are two reports on myoclonus associated with spinal anesthesia (2,3), but the time of onset, the pattern, rhythmicity and duration were quite different in this case.

At the present time there is no clear understanding of the mechanism of sleep-related myoclonus, nor of the unusual response that we observed during spinal anesthesia. Physiologic changes commonly seen both during sleep and at this stage of spinal anesthesia are believed to be involved in inducing this type of move-

ment. These changes include inhibition of an inhibitory pathway from the cerebral cortex (4). During sleep the extrapyramidal tract is depressed (5), whereas spinal anesthesia blocks more intensively the inhibitory neurons in the posterolateral column (6,7). This results in isolation of spinal interneurons that, being free from inhibition, become excited. In our patient, myoclonic movement initiated on the nondependent side of the lateral position on two separate occasions. This also suggests an uneven distribution of local anesthetic drug in the spinal cord.

There is evidence that might indicate an effect on motor neuron activity, especially its periodic excitation, with increased sympathetic activity (8,9). In our case a cyclic variation of arterial pressure was seen, indicative of periodic sympathetic activity, but we found no further evidence to correlate sympathetic activity and motor neuron activity in the mechanism of the type of movement we saw during sleep and during spinal anesthesia in this patient.

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Sympathetic Blockade and Tourniquet Pain in Surgery of the Upper Extremity

Richard-Salim Farah, MD, and P. Sebastian Thomas, MD

Introduction

Orthopedic procedures on an extremity are frequently performed using pneumatic tourniquets to decrease blood loss and provide a bloodless surgical field. In many instances surgery (especially of the upper extremity) is performed using regional anesthesia. Unfortunately, tourniquet pain, usually experienced 30 to 60 min after inflation of the tourniquet (despite surgical anesthesia) (1-4), limits the usefulness of some regional blocks. This disturbing phenomenon continues to occur despite the use of inflation pressures lower than those used several decades ago (5-8).

Various methods used to decrease or alleviate tourniquet pain during IV regional anesthesia have generally been unsatisfactory. The use of double tourniquets with inflation of the distal and deflation of the proximal tourniquets at the onset of pain only temporarily relieves and does not prevent the pain (1). Transcutaneous electrical nerve stimulation (TENS) has proved equally unsatisfactory in the relief of tourniquet pain (9). Small amounts of intravenous narcotics have also been used with variable success.

The authors investigated the hypothesis that tourniquet pain experienced during upper extremity surgery is mediated via sympathetic fibers. We studied 12 patients undergoing surgery under IV regional anesthesia in combination with stellate ganglion block.

Materials and Methods

Twelve adult outpatients (ASA categories I-III) between the ages of 19 to 51 years, scheduled for elective upper extremity surgery requiring pneumatic tourniquets, were selected (Table 1). The protocol was

approved by the Institutional Review Board for the Protection of Human Subjects and informed consent was obtained.

After placement of an intravenous catheter in the nonoperative arm and appropriate monitors attached, a pre-stellate ganglion block thermographic study was performed on the operative lower arm and hand using liquid crystal thermography (10). A stellate ganglion block was then performed on the operative side with 7 ml of 0.25% bupivacaine, using an anterior approach. Adequate sympathetic blockade was ascertained by development of ipsilateral Horner's syndrome (11) and a positive thermographic study 6 to 18 min after completion of the block.

Patients were then transferred to the operating room, where pretested double tourniquets were applied. After satisfactory exsanguination of the extremity using an Esmarch bandage, both tourniquets were inflated. Intravenous regional anesthesia was then induced using 40-50 ml 0.5% lidocaine. The distal tourniquet was deflated and the proximal tourniquet maintained at 250-300 mm Hg on completion of the lidocaine injection.

The presence of tourniquet pain was subjectively assessed by the patients throughout the procedure. Time of onset of the pain from inflation of the proximal tourniquet was noted, as was the amount and type of sedative and/or narcotic needed to maintain patient comfort.

Results

The results from two of the participating patients were discarded. In one patient, the tourniquet failed and the second patient claimed he had no anesthesia at the time of incision and general anesthesia was induced. Sympathetic block of the upper extremity was present in all patients, as demonstrated by thermography and a positive Horner's syndrome (Table 1). The remaining ten patients experienced tourniquet

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Table 1. Patient Data

Patient No.	Age (yr)	Location of surgery	Horner's	Thermography	Stellate ganglion block to tourniquet inflation (mins)	Tourniquet pressure (mm Hg)	Tourniquet time to pain (mins)	Sedation or narcotic
1	40	Distal ulna	+	+	12	300	57	S
2	42	Distal ulna	+	+	28	300	10	S,N
3	50	Hand	+	+	37	250	36	S,N
4	28	Wrist	+	+	22	250	20	S
5	32	Hand	+	+	20	250	47	—
6	43	Finger	+	+	15	300	35	S,N
7	43	Finger	+	+	35	250	40	S,N
8	34	Finger	+	+	21	250	31	—
9	19	Wrist	+	+	25	250	21	—
10	51	Finger	+	+	43	250	20	S,N

S, Sedative (diazepam).

N, Narcotic (fentanyl).

+, present; —, absent.

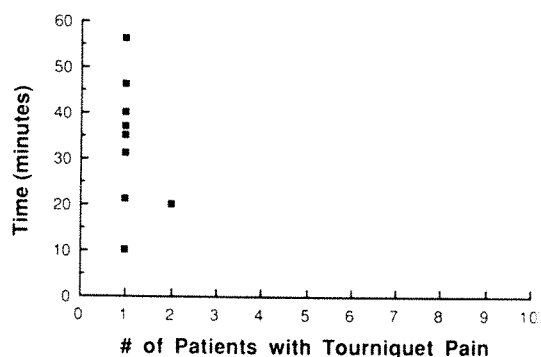


Figure 1. Time of onset of tourniquet pain in 10 patients.

pain at a mean time of 31.7 min, with a range of 10 to 57 min (Fig. 1).

Discussion

Tourniquet pain occurred in the ten patients included in the study. A number of techniques have been employed to demonstrate blockade of the sympathetic nervous system, including sweat test, psychogalvanic reflex, skin resistance, and thermography. Objective confirmation of sympathetic denervation of the upper extremity can be ascertained with great accuracy by measuring temperature before and after the block (12). The increase in temperature of the forearm, hand, and fingers demonstrated thermographically confirmed the presence of sympathetic blockade in our subjects.

The onset of tourniquet pain occurred during the surgical procedure. Prior experience in our Pain Treatment Center has indicated that the duration of Horner's syndrome is similar to alterations in temperature measured thermographically. The continued presence of ipsilateral Horner's syndrome into the post-operative period, therefore, is taken as confirmatory

evidence of persistence of sympathetic block at the time of onset of tourniquet pain. In addition, the duration of sympathetic blockade following 0.25% bupivacaine, in the range of 3 to 4 hr and can last up to 8 to 10 hr (13). The presence of ipsilateral Horner's syndrome and positive thermography, therefore, was taken as evidence of the adequacy of sympathetic blockade. Because the time of onset of tourniquet pain is similar to that reported by others, it may be assumed that the sympathetic blockade did not significantly alter this latent period.

Tourniquet pain associated with intravenous regional anesthesia is a common occurrence. Indeed, that is one of the main factors limiting its use in prolonged procedures. On this basis, we did not feel it was necessary to include a control group.

Approximately 30 years ago, Cole (5) suggested that tourniquet pain was caused by compression or possibly by ischemia of large nerves and believed it was an autonomic pain sufficiently intense to penetrate the regional block. Egbert and Deals (6) later disputed Cole's assumptions and proposed that the pain was due to an inadequate concentration of tetracaine, leaving the large fibers unblocked. They presumed that the pressure pain fibers were larger than those transmitting pricking pain (i.e., cutaneous pain sensation). On the other hand, DeJong and Cullen (2) implicated amyelinated C-fibers ("slow" pain fibers) as being responsible for tourniquet pain.

Tourniquet pain is currently thought to be mediated by unmyelinated "slow" conducting C-fibers that traverse the sympathetic trunks before entering the spinal cord above the level of the block. This "slow" pain is usually inhibited by earlier arriving "fast" pain impulses from myelinated A- δ -fibers. Tourniquet compression of the limb causes loss of conduction in large fibers before affecting the smaller C-fibers. After

about 30 min of tourniquet compression, the A- δ -fibers are blocked, thereby removing the inhibition from the still functioning small C-fibers (3).

The liquid crystal thermography used in this study utilizes cholesterol crystals that change color according to surface temperature. It is a noninvasive procedure used to document the presence of sympathetic blockade.

In summary, though our data does not explain the mechanism of tourniquet pain, they eliminate the sympathetic pathway as being involved. The possibility of ischemia of the somatic nerves as a cause for the pain should be investigated.

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Intravenous Lidocaine: Optimal Time of Injection before Tracheal Intubation

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The circulatory stimulation accompanying laryngoscopy and tracheal intubation and its attendant potential hazards are well recognized. Many methods to attenuate this stress response have been studied, among which intravenous (IV) lidocaine has been popular, probably because of its theoretical advantages of suppressing cough reflex (1,2), preventing increases in intracranial pressure (3), attenuating circulatory responses (4), and its antiarrhythmic properties (5).

Abou-Madi et al. (6), in comparing two doses of intravenous lidocaine (0.75 and 1.5 mg/kg), found that the higher dose was more effective in attenuating circulatory responses to tracheal intubation. The time of injection of IV lidocaine for this purpose has, however, been either not clearly specified (6) or chosen on an empirical basis (7). There has been no evaluation of the optimal time of injection of IV lidocaine for the attenuation of circulatory responses secondary to tracheal intubation. We undertook this study to provide such data.

Methods

Seventy adult patients, ASA class I-II, ages 27 to 70, with no previous history of hypertension, and undergoing elective noncardiac surgery requiring intubation, were admitted to the study. Institutional approval was obtained for the study. These patients were randomly divided into five groups of 14 patients each. Groups I, II, III, and IV received lidocaine, 1.5 mg/kg IV 1, 2, 3, and 5 min before intubation, respectively. Lidocaine was injected as a single bolus over a period of less than 5 seconds. Group V served as the control and received no IV lidocaine.

All patients received morphine, 0.10 mg/kg and

perphenazine, 0.05 mg/kg IM 1 hr before induction of anesthesia. Patients were given *d*-tubocurarine, 0.04 mg/kg 5 min before intubation, followed by thiopental, 4.0 mg/kg and succinylcholine, 1.5 mg/kg IV 2 min before intubation. All intubations were performed by two experienced anesthetists. Patients in whom the duration of laryngoscopy was greater than 15 sec were excluded from the study.

Heart rate (HR), systolic blood pressure (SBP), mean blood pressure (MBP), and diastolic blood pressure (DBP) were monitored by an automatic blood pressure cuff (Datascope) before induction (baseline values) and then at 1-min intervals throughout induction and for 5 min after intubation.

Changes in each hemodynamic variable after intubation were based on the differences between baseline values and values obtained 1 min after intubation. Mean values $\pm$ one SD are reported for each group. Differences between groups were evaluated using one-way analysis of variance followed by Duncan's multiple-range test. $P < 0.05$ was considered statistically significant.

Results

There were no statistically significant differences between the five groups in age, sex, or ASA classification. Results are shown in Table 1, and Figures 1 and 2. Changes in HR and blood pressure (BP) were greatest 1 min after intubation. The 1-min postintubation values were, therefore, used to compare with the baseline values to determine if the increase was statistically significant. These values were also used to determine intergroup differences. When compared with baseline values, increases in SBP, MBP, DBP, and HR after intubation were not significantly different in patients given IV lidocaine 3 min before intubation (group III), but they were significantly above baseline levels in patients given lidocaine 1 min (group I) ($P < 0.05$), 2 min (group II) ($P < 0.05$), and 5 min (group IV) ($P < 0.05$) before intubation or in those not given lidocaine at all (group V) ($P < 0.05$). When

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Table 1. Hemodynamic Data

Variables	Patient groups				
	I	II	III	IV	V (Control)
Time of lidocaine administration before intubation (min)	1	2	3	5	—
SBP: Baseline	131 ± 25	133 ± 19	137 ± 17	128 ± 13	136 ± 13
1 min after intubation	163 ± 34	162 ± 20	149 ± 26	159 ± 18	174 ± 23
Increase	32 ± 21*	29 ± 20*	12 ± 21	31 ± 20*	38 ± 19*
MBP: Baseline	99 ± 19	102 ± 17	105 ± 16	99 ± 13	106 ± 14
1 min after intubation	129 ± 26	129 ± 17	116 ± 17	126 ± 18*	138 ± 17
Increase	30 ± 22*	27 ± 15*	11 ± 15	27 ± 22*	32 ± 15*
DBP: Baseline	77 ± 18	79 ± 11	86 ± 13	80 ± 10	83 ± 8
1 min after intubation	106 ± 29	108 ± 17	95 ± 14	102 ± 14	109 ± 15
Increase	29 ± 23*	29 ± 15*	9 ± 14	22 ± 15*	26 ± 16*
HR: Baseline	72 ± 14	75 ± 13	80 ± 15	76 ± 11	77 ± 16
1 min after intubation	100 ± 20	99 ± 14	92 ± 15	98 ± 6	102 ± 17
Increase	28 ± 17*	24 ± 15*	12 ± 10	22 ± 13*	25 ± 13*

*Postintubation increase significantly different from baseline $P < 0.05$.

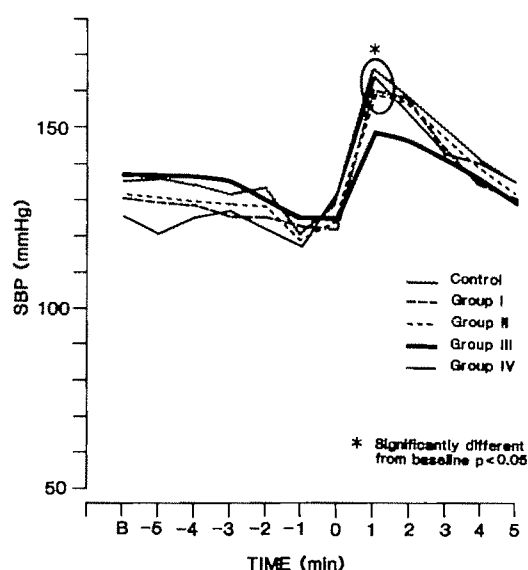


Figure 1. Changes in systolic blood pressure (SBP). B, Baseline. Negative times represent minutes before intubation. 0, time of intubation. Positive times represent minutes after intubation.

the data were further compared among the five groups, the 1-min postintubation increases in group III were found to be significantly less than in the other groups ($P < 0.04$). No side effects of lidocaine were noted.

Discussion

It is well known that laryngoscopy and tracheal intubation are accompanied by increases in HR and ABP (8). In most patients these changes are well tolerated. In certain groups of patients, such as those who at risk for developing arterial hypertension (9) or myocardial ischemia (10), such changes may be detrimen-

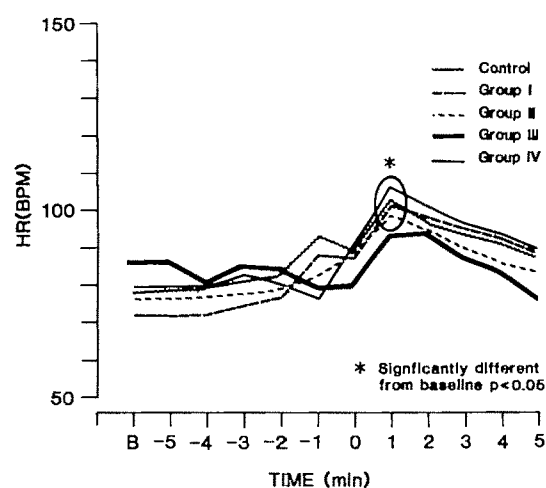


Figure 2. Changes in heart rate (HR). B, Baseline. Negative times represent minutes before intubation. 0, time of intubation. Positive times represent minutes after intubation.

tal. The precise mechanism by which these changes are produced is uncertain but probably involves intense sympathetic discharge caused by stimulation of the upper respiratory tract (11,12).

Lidocaine has been a popular agent for attenuating circulatory responses associated with tracheal intubation. It has been used as a lidocaine gargle for oropharyngeal anesthesia (13), as a lidocaine aerosol for intratracheal anesthesia (14), or as an intravenous bolus for systemic anesthesia (4). Intravenous lidocaine, in particular, has been found to suppress the cough reflex (1,2), to prevent increases in intracranial pressure (3), to attenuate circulatory responses (4) and to possess antiarrhythmic properties (5).

The best dose of intravenous lidocaine for atten-

uation of circulatory responses to laryngoscopy and intubation has been established at 1.5 mg/kg (6). The time of injection of IV lidocaine before intubation is, however, not well documented, varying, on an empirical basis, from 1 to 3 min before intubation (6,15).

Our study shows that IV lidocaine at a dose of 1.5 mg/kg given 3 min before intubation offered statistically significant attenuation of increases in all of the four hemodynamic variables. IV lidocaine given at 1, 2, and 5 min offers no statistically significant protection against increases in SBP, MBP, DBP, and HR. The attenuation of circulatory response to tracheal intubation occurred only when the IV lidocaine was given 3 min before intubation.

Intravenous lidocaine may suppress circulatory responses to tracheal intubation by increasing the depth of general anesthesia. Lidocaine blood levels of 3–6 $\mu\text{g/ml}$ are known to potentiate the effects of nitrous oxide anesthesia in humans (16). Lidocaine also has direct cardiac depressant and peripheral vasodilating effects. The blood level for these direct effects has been generally accepted to be 1.5–6 $\mu\text{g/ml}$.

We did not measure lidocaine blood levels in this investigation. Ideally, it would be desirable to correlate the clinical effect of lidocaine with blood levels. However, such a correlation may not be appropriate because the mechanism by which IV lidocaine suppresses pressor responses is still unclear. Also, blood level may not necessarily reflect tissue levels. Furthermore, Patel et al. (18) have reported that lidocaine blood concentration peaked within the first minute after an IV bolus, a time interval far too early for any study to observe any clinical effect. Our assumption that blood levels do not correlate with clinical effects is further substantiated by Safwat et al. (19), who found that plasma levels of propranolol did not correlate with its clinical effect of hemodynamic control when used before rapid sequence induction of anesthesia and tracheal intubation.

We conclude that IV lidocaine at 1.5 mg/kg attenuates increases in HR and ABP only when given 3 min before intubation, and offers no protection against postintubation hemodynamic changes when given at 1, 2, or 5 min before intubation.

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Postoperative Quadriplegia after Spinal Fusion for Scoliosis with Intraoperative Awakening

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Neurologic complications, although rare, may follow scoliosis correction by spinal fusion (1,2). The incidence of acute neurologic complications during spine fusion may vary, with the population treated and the procedure performed, from 0.7% to 5.0% (2,3). The etiology of cord damage during spinal fusion remains unclear, but may involve vascular compromise associated with mechanical deformation (1,4-6).

Intraoperative monitoring of spinal cord function during scoliosis correction has been recommended as a means of detecting early neurologic deficits that can be reversed by reduction of vertebral distraction or removal of supporting rods (3,6-11). Wake-up techniques and recording of somatosensory evoked potentials (SSEPs) are the only current means for monitoring spinal cord integrity during scoliosis surgery (3,6-12). Recently, postoperative paraplegia has been observed despite the recording of normal intraoperative SSEPs. As SSEP monitoring continues to be a research tool that is not universally available, intraoperative awakening has remained an important modality for testing cord integrity after scoliosis correction since its introduction in 1973 (11). Permanent quadriplegia after successful intraoperative awakening during spine fusion for scoliosis is now reported.

Case Report

A 16-year-old, 50-kg male with a 3-yr history of progressive idiopathic scoliosis was scheduled to undergo elective posterior spine fusion with Harrington rod instrumentation. Two years before surgery, the patient complained of right lower extremity weakness. Lumbar puncture, thoracolumbar myelogram, and

computerized tomograms of the thoracolumbar spinal cord were normal at that time. The lower extremity weakness resolved with physical therapy and gradual resumption of activity.

On admission for surgery, pulmonary function testing demonstrated a vital capacity of 80% of predicted. X-ray films showed a 45° left lower thoracic spinal curve with a 32° compensatory right lumbar curve. Preoperative neurologic examination was normal. Arterial blood gas tensions, serum chemistries, and urinalysis were within normal limits. Hemoglobin was 13 g/100 ml after donation 6 weeks before surgery of two units of whole blood for autologous transfusion.

The evening before surgery, the patient developed acute urinary retention, attributed to preoperative anxiety, which finally required catheter drainage of 650 ml of urine. No further difficulty in voiding occurred. Neurologic examination was unchanged. The patient was coached on the conduct of intraoperative awakening during spine fusion to evaluate spinal cord integrity and was assured of a pain-free course and rapid reanesthetizing after movement of the lower extremities in response to commands and pinpricks.

The patient was premedicated with morphine sulfate, 10 mg, and scopolamine, 0.3 mg IM, and arrived in the operating room somnolent but arousable. An 18-gauge IV cannula was inserted and IV induction of general anesthesia was carried out, after *d*-tubocurarine, 3 mg, at 0800 hours with thiopental, 200 mg, followed by succinylcholine, 80 mg, and morphine sulfate, 5 mg. A 7.0-mm endotracheal tube was inserted, and mechanical positive pressure ventilation with a minute volume of 5.5 L was instituted. The patient was moved from the supine to the prone position on a Relton-Hall operative frame, with careful padding of the head, shoulders, and extremities. An additional 14-gauge IV cannula was inserted for warmed IV fluid and colloid administration. Additional intraoperative monitors included esophageal stethoscope, blood pressure cuff, radial artery Doppler, finger plethysmograph, electrocardiogram, and

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Table 1. Conditions Predisposing to Neurologic Injury during Scoliosis Correction^a

1. Kyphosis
2. Severe scoliosis (>50° curve)
3. Congenital scoliosis
4. Scoliosis associated with neurologic deficits
5. Scoliosis associated with neurologic deficits acquired during skeletal traction

^aReprinted with permission from MacEwen et al. (2).

rectal thermister. General anesthesia was maintained with 10 mg morphine sulfate in incremental doses, 0.2–0.5% inspired halothane, and 60% N₂O in O₂, plus an additional 24 mg of *d*-tubocurarine. The systolic blood pressure was maintained at 85 torr during surgical exposure of the spine, decorticating osteotomies, and bone graft harvesting. A normal blood pressure of 110–120/65–75 mm Hg was restored for spinal distraction and Harrington rod insertion between T5 and L1. Measured operative blood loss was 2000 ml. This was replaced with 2500 ml of lactated Ringer's solution in 5% dextrose, 2 units of autologous whole blood, and 2 units of banked blood. After hardware application and spine straightening, halothane and N₂O were discontinued, and, within 15 min the patient responded to pinpricks with rapid withdrawal of each foot, and to verbal commands with appropriate movements of each foot. The patient was quickly reanesthetized with thiopental, 50 mg IV, and 60% N₂O in O₂. No further muscle relaxants were administered. The incision was closed, the residual neuromuscular block was reversed with neostigmine, 2.5 mg IV, and atropine, 1.2 mg, and the patient was moved to the supine position for extubation.

When admitted to postanesthetic recovery at 1110 hours, the patient moved both lower extremities spontaneously and remained somnolent but responsive and comfortable. At 1630 hours, the patient complained of numbness in the lower extremities. Vital signs had remained stable and the urine output was 75 ml/hr. Physical examination showed no spontaneous movement of the lower extremities, a fluctuating level of paraplegia from T6 to T8, no deep tendon reflexes or clonus in the legs, and a patulous anal sphincter. An arterial blood sample had a pH of 7.43, a PaO₂ of 150 mm Hg, a PaCO₂ of 37 mm Hg, and a base excess +2 mEq/L labile breathing 40% O₂. Dexamethasone, 10 mg was administered IV, and the patient was returned to the operating room for immediate removal of the rod and reduction of spinal distraction. This was done uneventfully under endotracheal general anesthesia at 1745, after which he was readmitted to postanesthetic recovery at 1930 hours.

Table 2. Orthopedic Procedures Predisposing to Neurologic Injury during Scoliosis Correction^a

1. Preoperative skeletal traction
2. Spinal osteotomy
3. Use of Harrington instrumentation to gain correction in congenital scoliosis
4. Use of Harrington instrumentation to gain further correction after skeletal traction

^aReprinted with permission from MacEwen et al. (2).

By 2000 hours, the patient was awake, oriented, and responsive. Neurologic examination showed flaccid quadriplegia with a T1 sensory level. Deep tendon reflexes were 1+ out of 4+ in the upper extremities, and unobtainable in the legs. Re-examination at 2200 hours showed T3 flaccid quadriplegia. Cranial nerve function remained intact. Arterial blood gas tensions and minute volume of ventilation remained within normal limits. Cervical neck radiographs showed no evidence of cervical subluxation or vertebral fracture.

At 2400 hours, a lumbar myelogram was performed and demonstrated complete block to contrast spread at L1–2 presumed to be secondary to a postoperative epidural hematoma.

At 0130 hours, a cervical myelogram by a cisternal tap showed a markedly widened lower cervical and upper thoracic spinal cord with associated compromise of the subarachnoid space. Cerebrospinal fluid was grossly clear with a glucose of 76 mg/100 ml, a protein of 281 mg/100 ml (laboratory normal 20–35 mg/100 ml), and a differential cell count with 50% leukocytes and 50% erythrocytes. Immediate cervical laminectomy to decompress a suspected intramedullary cord tumor was recommended.

At 0245 hours, the patient was anesthetized for the third time with the same anesthetic agents (except morphine) for C3 to C7 cervical laminectomy, which disclosed a large intramedullary cervical cord cyst consistent with syringomyelia. The syrinx was drained by shunt to the thoracic subarachnoid space. Cervical laminectomy was completed at 0930 hours. The tracheal tube remained in place until 1100 hours, when the maximum minute volume of ventilation was 10 L/min, forced vital capacity 700 ml, and inspiratory force –24 cm H₂O. Neurologic examination was unchanged, with a high thoracic level of flaccid quadriplegia.

Four days after cervical laminectomy, computed tomograms of the spinal column showed a dilated lower cervical cord, moderately enlarged upper and midthoracic cord, and widened lower thoracic spinal cord and conus medullaris consistent with extensive syringomyelia. Results of neurologic examination at this time were unchanged. Eight days after cervical

laminectomy, lumbar laminectomy with terminal ventriculostomy to drain the cord conus into the spinal subarachnoid space was performed under a general anesthetic similar to the ones described.

Discussion

Certain well known preexisting conditions carry an increased risk of neurologic injury after scoliosis correction (Table 1) (2). Certain orthopedic procedures in themselves may also predispose patients to an increased risk of neurologic injury after scoliosis surgery (Table 2) (2,13,14). Despite the advent of intraoperative cord monitoring by wake-up techniques or SSEPs and the identification of existing conditions and orthopedic procedures that may predispose patients to neurologic injury, a small number of patients with idiopathic scoliosis undergoing ordinarily low-risk corrective procedures continue to suffer neurologic complications (15). No studies comparing the sensitivity of intraoperative wake-up and SSEPs have been conducted.

Intraoperative awakening with observation of limb movement as initially described by Vauzelle et al. (11) has proved very valuable in the early recognition of reversible sensorimotor deficits in a large population of young patients with nonparalytic scoliosis. Unlike SSEPs, the wake-up technique does not require complex electrical equipment (nerve stimulator, electroencephalogram, electromyograph with averager, amplifier, or oscilloscope) or technical expertise for interpretation (7). Unlike SSEPs, the successful wake-up indicates significant cortical integration and preservation of dorsal column and motor tract functions. Wake-up is not seriously affected by anesthetic agents, hypotensive anesthesia, or electrical interference. Unlike SSEPs, false-negative wake-ups have never been reported. In fact, intraoperative wake-up has been suggested to corroborate frequently occurring false-positive SSEPs and to definitely exclude neurologic deficits (15).

Certain hazards of wake-up techniques do exist. These include recall, pain, emotional damage, accidental tracheal extubation, air embolism via exposed epidural veins, and rod dislocation or fracture during coughing (7). These hazards have not, however, complicated the reported series (8,10).

Severely retarded patients, infants, and young children are not good candidates for intraoperative awakening and might benefit from SSEPs during scoliosis correction. Paraplegic patients are not good candidates for either wake-up or SSEPs, but certainly need intraoperative sensorimotor monitoring to prevent extension of existing neurologic deficits. For meaningful

SSEPs in paraplegics, preoperative identification of accessible areas distal to cord traction where nerve stimulation produces adequate cortical activity would be necessary.

In the case reported here, delayed paraplegia with subsequent quadriplegia after posterior spine fusion was unusual in that the patient was assumed to have idiopathic scoliosis, not syringomyelia. The neurologic deficit did not manifest itself during intraoperative awakening; however, it did progress despite immediate rod removal. With the diagnosis of syringomyelia confirmed at cervical laminectomy, the clinical presentation of the neurologic injury became clearer. Mild-to-moderate scoliosis is a common presenting manifestation of syringomyelia and has been reported in from 20 to 87% of patients (13,16). Spinal distraction, fusion, and Harrington instrumentation carry a significant risk of neurologic damage in patients with scoliosis and associated syringomyelia (16-18). Three cases of permanent paraplegia have been reported after correction of syringomyelia-associated scoliosis (16,18). Permanent quadriplegia has not been reported after correction of either idiopathic scoliosis or syringomyelia-associated scoliosis. Whether intraoperative monitoring of SSEPs would have prevented neurologic injury in this case is uncertain. Despite successful wake-up, loss of SSEPs or intermittently abnormal SSEPs may have directed earlier rod removal with further diagnostic studies leading to decompressive cervical laminectomy. As noted, false-negative SSEPs have now been recorded from a patient who was paraplegic postoperatively (15).

In conclusion, preexisting neurologic illnesses associated with scoliosis may have clinical signs so subtle as to be undetected by physical or neuroradiographic examinations. A small percentage of patients with presumed idiopathic scoliosis and no family history of neuromuscular disease, neurofibromatosis, or mesenchymal disorder (Marfan's syndrome, mucopolysaccharidosis, glycogen storage disease, or rheumatoid arthritis) may present with scoliosis secondary to syringomyelia or intraspinal neoplasm (16,19,20). Neurologic symptoms may be absent or minimal in these patients. If present, these patients must be thoroughly evaluated before scoliosis surgery. Scoliosis correction in these patients may extend a syrinx, fragment a tumor, or compromise a vascular malformation with devastating, often delayed neurologic sequelae undetected by intraoperative awakening (16,18).

As this case demonstrates, intraoperative wake-up may not always prove an absence of neurologic damage during scoliosis repair. Future reports and studies that compare the sensitivity of intraoperative wake-up and SSEPs in detecting neurologic injury during

Harrington rod surgery are recommended. To date, only one case of false-negative intraoperative SSEPs has been reported (15). The case reported here represents the first known false-negative wake-up test.

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Malignant Hyperthermia in a Three-Month-Old American Indian Infant

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To our knowledge, the development of malignant hyperthermia (MH) after the administration of recognized triggering agents has not been reported in a patient younger than 6 months of age. We present a case report documenting its occurrence in a 3-month-old infant.

Case Report

A 2,100-g full-term American Indian female was found at birth to have multiple congenital anomalies, including micrognathia, cleft palate, talipes equinus, and arthrogryposis. At 1 week of age, she was transferred to Duke University Medical Center because of periodic apnea and dysphagia. Further evaluation revealed a tethered cord, T12-L1 syrinx, gastroesophageal reflux, and a depressed gag reflex. The dysphagia and periodic apnea persisted for the next 6 weeks, necessitating intermittent tracheal intubation and ventilation. At 7 weeks, under general anesthesia, a central catheter was placed for parenteral nutrition. After 0.1 mg IV atropine and preoxygenation, awake tracheal intubation was performed without difficulty. Anesthesia was maintained with halothane, pancuronium, and O₂. The perioperative course was uneventful.

Over the next 6 weeks she improved, but continued to have difficulty with swallowing. At 3 months old, weighing 3.16 kg, she was returned to the operating room for a feeding gastrostomy under general anesthesia. On arrival, she was afebrile and vital signs were stable. After 0.1 mg IV atropine and preoxygenation, awake intubation was performed with some difficulty. After intubation, the heart rate was 170 beats/min, blood pressure 90/50 mm Hg, and the esophageal temperature was 37.3°C. Nitrous oxide, oxygen, and halothane were administered, and 0.6

mg/kg atracurium was given IV. Over the next 5 min, the chest compliance deteriorated; the peak inspiratory pressure as monitored on the gauge of the volume-cycled ventilator increased to 40 cm H₂O from 20 cm H₂O. The heart rate increased to 205 beats/min, and the end-tidal CO₂ (P_ECO₂) increased from 45 to 70 mm Hg (IL2000 Capnometer; Instrumentation Laboratory, Lexington, MA.). Breath sounds were rechecked and found to be clear and bilaterally equal. The tracheal tube was suctioned without improvement. At this time, the surgeon, who had prepared the abdomen and draped the baby, commented that the abdomen was "extremely rigid". After quickly confirming the absence of a twitch response on the ulnar nerve stimulator, an orogastric tube was passed and the stomach decompressed without improvement. The drapes were removed and diffuse rigidity was noted. Halothane was immediately discontinued, and 100% oxygen was administered using a fresh disposable nonrebreathing circuit. On withdrawal of halothane, chest wall compliance improved, with peak inspiratory pressures decreasing by 10–15 cm H₂O. Sodium bicarbonate, 1 mg/kg and dantrolene sodium, 1 mg/kg were given IV. Over the next 10 min, the rigidity disappeared, and the peak inspiratory pressure and P_ECO₂ returned to preanesthetic values. The maximal esophageal temperature recorded was 38°C, noted at the time of diffuse rigidity. Heart rate and blood pressure remained moderately elevated above baseline levels. A 22-gauge catheter was placed in a radial artery and a urinary catheter was inserted. The initial arterial blood specimen obtained 12 min after diagnosis of MH and treatment had a pH of 7.52, a PaCO₂ of 28 mm Hg, a PaO₂ of 440 mm Hg, and a base excess of -1.5 mEq/L.

No surgery was performed, and the baby was taken to the pediatric intensive care unit in stable condition. A venous blood sample obtained immediately on arrival in the pediatric intensive care unit showed that the CPK level had increased from a preoperative level of 46 international units (IU) (normal 0–160) to 492 IU. Several episodes of tachycardia and hypertension,

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unassociated with hypercarbia or acidosis, resolved after a further dose of 1 mg/kg dantrolene IV. Blood gas tensions and chemistries remained stable. The peak CPK level was 1470 IU at 6 hr postoperatively. Dantrolene was repeated at 1 mg/kg IV every 6 hr.

After 36 hr, without signs of recrudescence and while still intubated and receiving dantrolene, gastrostomy was performed under general anesthesia with MH precautions. Her anesthetic consisted of 7 μ g/kg IV fentanyl, 0.6 mg/kg IV atracurium, and 50% N₂O in oxygen. The patient did well, and there were no signs of MH. CPK levels remained normal postoperatively, and dantrolene was discontinued 24 hr later. She was subsequently successfully extubated and transferred to the ward for further care.

At 13 months of age, the patient underwent correction of talipes equinus and cleft palate repair. Anesthetic management consisted of pretreatment with 1 mg/kg IV dantrolene before induction, followed by thiopental, atracurium, nitrous oxide, oxygen, and fentanyl. Her intra- and postoperative course was uneventful.

The family history is negative for previous episodes of malignant hyperthermia, and diagnostic testing was refused.

Discussion

This case is remarkable for the occurrence of MH in a 3-month-old child. The infant exhibited some of the classic signs during her second anesthetic. Shortly after exposure to halothane, she developed a marked increase in P_{ECO_2} while ventilation was being mechanically controlled. This increase is often the earliest sign of MH (1). Her core temperature increased from 37.3 to 38°C over the 15 min after administration of halothane and atracurium. During this time she also developed diffuse rigidity, tachycardia, hypertension, and a slightly elevated temperature, all recognized features of MH (2,3). Most signs abated after withdrawal of the triggering agent and before dantrolene therapy. This is sometimes seen after only a brief administration of halogenated inhalation anesthetics (4). Complete regression of clinical signs of MH followed the administration of dantrolene. The low dose (1 mg/kg) of dantrolene used in this case was chosen because the clinical signs had already abated. This does not imply that the larger dose of 2.5–3.5 mg/kg should not be used in other circumstances; this dosage is based on excellent studies in older humans (5,6). A 10-fold increase in CPK levels has been suggested as being diagnostic of MH in otherwise unexplainable situations (7); our patient's CPK levels increased 30-fold over preoperative levels.

The overall incidence of MH has recently been reported to be 1/18,000 in cases in which succinylcholine has, as in our case, not been used (8). The maximum incidence lies between the ages of 3 and 30 years. A few cases have been reported in children as young as 6 months (9,10). A probable diagnosis of MH was also made in a premature infant born by cesarean section, who exhibited marked muscle rigidity and developed elevated CPK levels with myoglobinuria (11).

Despite the young age of our patient, there were some important risk factors present that should have alerted us to the possibility of MH susceptibility. Disorders in tissues of mesenchymal origin have been associated with an increased incidence of MH (2), and our patient had several musculoskeletal disorders. Additionally, the patient was of Lumbee Indian descent. This particular population group appears to have a much higher incidence of MH susceptibility than does the general population (K. Sugioka, MD, personal communication).

The history of a previously unremarkable halothane anesthetic in our patient is consistent with the diagnosis of MH susceptibility. It has been shown that MH reactions occur in less than half of the MH-susceptible patients when exposed to triggering anesthetic agents (12). The reason for this is not known and may be related to stress factors (13). The multiple tracheal intubation attempts before our patient's MH crisis were certainly stressful to the baby. The previous intubation had succeeded after a single atraumatic laryngoscopy.

It is interesting to note that MH developed rapidly in our patient after the administration of halothane and atracurium. When the triggering agent is thought to be one of the inhalational agents, the onset is usually more insidious and may take hours, whereas when it develops after the administration of a muscle relaxant, typically succinylcholine, the onset occurs within minutes (14). One may, therefore, speculate as to whether atracurium would have triggered MH in our patient. Atracurium is incapable of triggering MH in an animal model (15), and there are no reports of its association with MH in humans. Ording and Nielsen (16) used atracurium in 40 patients during general anesthesia for diagnostic muscle biopsy for evaluation of MH status. There was no clinical or biochemical evidence of the onset of MH in any of these patients. Fifteen of the 40 patients were subsequently found by *in vitro* contracture tests to be susceptible to MH, and six were found to be equivocationally susceptible to MH.

In summary, we present a case report of a 3-month-old American Indian infant who developed MH after the administration of halothane and atracurium. This

has not previously been reported in such a young infant.

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Relationship between Esophageal Temperature Gradient and Heart and Lung Sounds Heard by Esophageal Stethoscope

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A popular technique for monitoring body temperature is measurement of esophageal temperature with either single temperature probes or esophageal stethoscopes with integral temperature probes. In this report, we investigate the size of the temperature gradient along the esophagus and its relationship to the heart and breath sounds heard through an esophageal stethoscope.

Methods

All temperatures were measured with Sheriden esophageal stethoscopes, model 5-13724, which contain a series 400 thermistor temperature probe. These esophageal stethoscopes have depth markings printed along their length, allowing accurate and repeatable positioning. The temperature probe is at the very tip of the esophageal stethoscope. The thermistor was connected to a Yellow Springs Instrument Company temperature monitor which could be read to $\pm 0.1^{\circ}\text{C}$.

Esophageal temperatures of 15 patients undergoing total hip or total knee replacement were measured. All patients underwent tracheal intubation, with the endotracheal tube cuff palpable in the suprasternal notch. Anesthesia was maintained with oxygen, 2 L/min, nitrous oxide, 3 L/min, and isoflurane. End-tidal CO_2 , measured by mass spectrometer, was maintained between 35 and 45 mm Hg.

After induction, an esophageal stethoscope was inserted for routine monitoring of temperature and breath and heart sounds. After the temperature had stabilized, usually at least an hour after induction, the position of best sounds was determined. Best sounds was defined as the best combination of breath sounds and heart sounds. Usually as the stethoscope was

progressively inserted, the breath sounds were loudest with no heart sounds audible, then a decrease in breath sounds with increasing heart sounds, and finally strong heart sounds with weak breath sounds. The position of best sounds was determined without observing the stethoscope depth so as to reduce bias. Once the position of best sounds was determined, the stethoscope was shifted up or down to the nearest depth marking. These markings start at 22 cm and are placed every 4 cm thereafter. All positions were measured relative to the upper central incisors. This maximum shift of 2 cm had very little effect on the sounds.

The stethoscope remained at this last position until the temperature stopped drifting; this temperature was recorded. The stethoscope was then inserted to a depth of 42 cm and the temperature again recorded after cessation of drift. Temperatures were measured in the same manner at depths of 38, 34, 30, 26, and 22 cm, skipping the depth of best sounds. The stethoscope was then returned to the position of best sounds (on the nearest depth calibration) and the temperature remeasured.

Results

The mean age, height, and weight of the patients appear in Table 1, along with the esophageal temperature at each distance from the upper incisors. Seven patients had best sounds at 26 cm, and 8 patients had best sounds at 30 cm. There was no statistical difference (unpaired *t*-test) between the weights and heights of these two groups. Two of five men and five of ten women had best sounds at 26 cm.

The difference in mean temperature between the position of best sounds and the other positions along the esophagus is shown in Figure 1. A positive distance corresponds to a position of greater depth relative to the position of best sounds. The difference in temperature between the position of best sounds and other positions ranged from -1.3°C to $+2.4^{\circ}\text{C}$. Four patients had temperatures 1.5°C or higher than those

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Table 1. Mean Age, Height, Weight and Esophageal Temperature (°C) vs Distance from Incisors in 15 Patients

	Age (yr)	Height (cm)	Weight (kg)	Distance (cm)					
				22	26	30	34	38	42
Mean	52	172	75	35.1	34.6	35.2	35.7	35.9	36.0
SD	21	9.4	20	1.35	1.08	1.07	1.09	1.10	1.11
SEM	5.5	2.4	5	0.35	0.28	0.28	0.28	0.28	0.29
Range	18-84	157-188	50-122	33.0-36.9	32.7-36.3	33.2-37.0	33.9-37.6	34.0-37.7	34.0-37.8

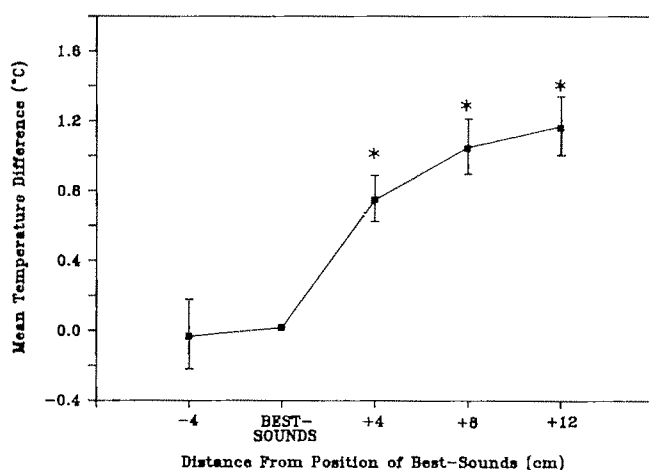


Figure 1. Mean and SEM of the difference in esophageal temperature from position of best sounds. Positive distance denotes direction toward stomach. * Indicates statistical significance at $P < 0.01$.

at the position of best sounds. Analysis of variance with repeated measures (BMDP P2V) and two-tailed Dunnett's test were used to determine the statistical significance of the temperature difference between the position of best sounds and other positions along the esophagus. There was no statistically significant difference in temperature between the position of best sounds and -4 cm. The temperature differences at positive positions were all statistically significant at $P < 0.01$. In seven patients (with best sounds at 26 cm) who had temperature measurements made at +16 cm, the increase in mean temperature between +12 cm and +16 cm was 0.06°C (NS, Student-Newman-Keuls test).

Discussion

The data as presented in Figure 1 are independent of the accuracy (offset) of the temperature measurements. Their validity depends only on the slope and linearity of the measuring system over a very small range of temperatures. The body temperatures of the patients were stable during the measurement period, as the mean difference in temperature between the two measurements at position of best sounds was 0°C .

The position of best sounds is the coolest location in the esophagus, as can be seen in Figure 1. However, 12 cm deeper, corresponding to a distance of 38-42 cm from the central incisors, the temperature is as much as 2.4°C higher. Deal et al. compared esophageal and rectal temperatures in six normal and eight asthmatic patients (1). Thermocouples were placed in the esophagus behind the trachea and behind the heart. In the most extreme test, the subjects were exposed to an inspired air temperature of approximately -17°C at rest and during exercise. Mean ventilation during exercise of the normals and asthmatics was 96.9 and 68.8 L/min, respectively. In both groups, the retrocardiac esophageal temperature maintained a constant relationship with the rectal temperature (both remained essentially constant), whereas the retrotracheal esophageal temperature fell progressively with time. Thus retrocardiac esophageal temperature is unaffected by even extreme airway cooling.

Severinghaus studied five patients and found that the coolest area of the esophagus was at the tracheal bifurcation (2). Whitby and Dunkin found temperature variations along the length of the esophagus as large as 6.5°C , with the minimum temperature 6-15 cm (mean, 10 cm) past the corniculate cartilages (3). No data were included on patient weight or height, although they reported that no connection could be established between site of minimum temperature and patient height or distance between cricoid and xiphisternum. They also reported large lateral temperature variations in some areas of the esophagus, i.e., temperature at a given depth varied depending upon whether the thermocouple contacted the left, middle, or right wall of the esophagus. No particular lateral orientation was consistently coolest. Lateral and longitudinal temperature variations became very small, and the maximum temperatures were recorded in the distal quarter of the esophagus 24-28 cm past the corniculate cartilages. No study correlated esophageal temperature to heart and lung sounds.

Accepting that the highest temperature in the esophagus is 12-16 cm past the position of best sounds, is this the correct temperature to measure? A measure

of core temperature should accurately reflect the temperature in the heart and brain. The brain is highly perfused and would be expected to follow heart (blood) temperature closely. Cooper and Kenyon reported the maximum temperature difference between the surface of the aorta and the retrocardiac esophagus to be 0.25°C in humans recovering from induced hypothermia (4). The retrocardiac esophageal temperature is offset by less than 0.2°C and lags by 1–3 min the right atrial blood temperature (5). It is worth noting that the outer surface temperature of the heart could differ from the inner surface (blood) temperature during open chest procedures.

The thermoregulatory consequences of core temperature arise from temperature-sensitive areas in the hypothalamus (6). Benzinger chose tympanic membrane temperature as the best indication of hypothalamic temperature and found it to precisely correlate with the thermoregulatory responses of the body. Tympanic membrane temperature and esophageal temperature are highly correlated and differ by about 0.2°C (7–9). However, tympanic membrane temperature is influenced by head skin temperature (9,10).

Rectal temperature has an unpredictable relationship to other deep body temperatures (2), can vary significantly with depth (2), and correlates badly with tympanic and esophageal temperature (7) and aortic surface temperature (4). Benzinger found rectal temperature to be unpredictable of thermoregulatory response (6). This is not surprising, because the rectum has no thermoregulatory mechanisms.

In summary: 1) The coolest area in the esophagus is where the best heart and lung sounds are auscultated. 2) Accurate esophageal temperature is measured behind the heart, 12–16 cm deeper than the position of best sounds. 3) Auscultation of esophageal sounds affords an easy method for determining cor-

rect temperature probe placement. 4) Measurement errors due to esophageal temperature probe positioning can be large enough to cause unnecessary therapeutic intervention and iatrogenic hyperthermia. 5) Esophageal stethoscopes with the temperature probe located at the auscultatory cuff should not be used. 6) Temperature probes should not be arbitrarily positioned in the esophagus. 7) Measurements (or reports) of heater-humidifier effects on body temperature, as measured by esophageal temperature, are likely to be in error due to direct airway heating of the esophagus, unless the temperature probe is known to be correctly placed.

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Letters to the Editor

Hypertensive Reaction to Indigo Carmine during Transurethral Resection of a Bladder Tumor

To the Editor:

Although it was almost 20 years ago that indigo carmine was reported as being associated with transient increases in blood pressure due to an increase in total peripheral resistance (1,2), only two cases of hypertension have been subsequently reported (3,4). We describe another case of hypertension due to indigo carmine during transurethral resection of a bladder tumor (TUR-BT).

An 85-yr-old man was scheduled for TUR-BT. Spinal anesthesia was induced, and blood pressure was stable at about 110/60 mm Hg throughout surgery. Surgery finished in 110 min, at which time 5 ml 0.8% indigo carmine was administered IV. Almost immediately, blood pressure increased to 170/90 mm Hg and within 5 min reached 190/90 mm Hg. Heart rate decreased simultaneously, from 55 beats/min to 45 beats/min. The patient had no chest pain or headache, and ECG showed no ischemic changes. Blood pressure gradually decreased to 165/80 mm Hg after about 10 min, and 45 min later it was 125/70 mm Hg. The post-operative course was uneventful.

Most urologists and anesthesiologists consider indigo carmine a safe diagnostic dye. Hypertension caused by indigo carmine can occur, however, and though generally not severe, it may be hazardous in patients with cardiovascular disease (1,2). In addition, in patients undergoing transurethral resection, as in our case, hypertension may be mistaken for, or may be augmented by the hypertension due to intravascular absorption of irrigating solution.

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A Simple Way to Monitor Inspired Oxygen Concentration in Nonbreathing Circuits

To the Editor:

I read with interest Claeys's Letter to the Editor describing a method of monitoring inspired oxygen concentration in a nonbreathing system (*Anesth Analg* 1986;65:1248-9). His technique involves connecting five different pieces of equipment. This increases the chances of disconnections and loss of small connectors.

For many years we have been using a simple approach to measure inspired oxygen concentration while using a nonbreathing system. We attach the 22-mm end of the oxygen sensor manifold of our oxygen analyzer (Critikon Oxychek Model Series 2000) directly on to the 15-mm anesthesia machine outlet (Ohio machines). The 15-mm connector of nonbreathing circuit easily fits onto the other end of the oxygen sensor manifold (Fig. 1). Although there are fewer connections, constant vigilance is still required.

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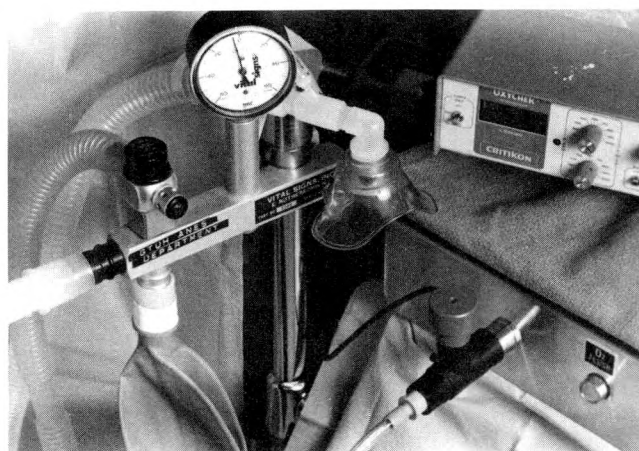


Figure 1. Oxygen analyzer manifold attached between anesthesia machine outlet and inspiratory limb of a nonbreathing circuit.

Blitz Intubation—A Useful Synonym

To the Editor:

A "rapid-sequence" or "crash" induction is often chosen for the patient with a full stomach at high risk for aspiration. However, both of these terms are somewhat unsatisfactory. "Rapid-sequence" is rather awkward whereas "crash" implies a lack of planning or control. Among the German anesthesiology community this is referred to as "Blitzintubation." "Blitz" is the German word for lightning and has entered the English language in several senses, including "blitzkrieg," but now also as an advertising blitz and a blitz in American football. In these connotations, "blitz" implies rapidity or suddenness, but with prior planning and control. Therefore, I would like to suggest that "blitz" intubation and "blitz" induction might make useful substitutes in the English language anesthesia literature for the terms "rapid-sequence" or "crash" intubation and induction.

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The opinions contained herein are the private views of the author and are not to be construed as reflecting the views of the US Army or the Department of Defense.

Physostigmine Reversal of General Anesthesia: Associated EEG Changes

To the Editor:

The report on the intraoperative use of physostigmine by Artru and Hui (1) was interesting and instructive. However, the authors left the impression that little had previously been known about the use of physostigmine during anesthesia. This impression is misleading and unfortunate because interested readers are thus discouraged from consulting the available literature.

In 1976, for example, Thomson described physostigmine as an adjuvant to neuroleptanalgesia in neurosurgical procedures (2). I can speak for our Department and say that for 12 years we have been using physostigmine for the "wake-up test" during Harrington rod operations and stereotaxic procedures. Numerous visitors became acquainted with this use of physostigmine.

It is also not quite exact to state (1) that EEG changes associated with physostigmine-induced awakening have not been reported previously in humans. Commin et al. (3) described changes in the EEG in several patients who woke after the administration of physostigmine. These authors reported that the changes of EEG are not always associated with behavioral changes after the administration of physostigmine. That the reverse is also true was reported by Pichlmayr and Lips (4) who found EEG but not behaviour

changes in humans after a premedicant dose of atropine. This indicates clearly that changes in the EEG cannot be used as reliable indicators of the anesthetic state of patients. Furthermore, Wilson (5), in writing about the effect of physostigmine in 1961, described the effects of toxic doses of atropine on the EEG of humans. Other relevant studies could be cited, but suffice to say that considerable knowledge on the use of physostigmine by anesthetists and on its properties has accumulated on this side of the Atlantic. For one reason or other, it seems that this information has not readily found its way to our colleagues elsewhere. Two books of studies on the central anticholinergic syndrome and physostigmine are available (6,7) and the third international symposium on this theme has been planned in Bonn.

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Inappropriate Attachment of PEEP Valve Causing Total Obstruction of Ventilation Bag

To the Editor:

We describe a life-threatening complication associated with the use of a disposable PEEP valve and manual ventilation bag.

Recently, while being mechanically ventilated with a Bear ventilator, a patient became agitated and developed cyanosis. An obstructing mucus plug within the lumen of the endotracheal tube was suspected. The patient was disconnected from the ventilator and manually ventilated on 100% oxygen with the Pulmanex ventilation bag (Life Design Systems, Milwaukee, WI) with a disposable, single-use PEEP valve attached to the expiratory port of the Pulmanex bag

(Vital Signs Inc., Tototowa, NJ). A suction catheter confirmed an endotracheal obstruction and the endotracheal tube was replaced. During resuscitation, the PEEP valve became disconnected from the Pulmanex manual ventilation bag. It was hurriedly replaced and, when attempts to ventilate the patient were resumed with the new endotracheal tube, complete obstruction to flow was noted. Despite repeated efforts at ventilation, the patient became deeply cyanotic and developed sinus bradycardia with ventricular extrasystoles. At this point, it was recognized that the PEEP valve was connected in the reverse position on the patient limb of the ventilation bag, thus creating complete obstruction to flow. The PEEP valve was replaced properly and the patient was subsequently ventilated easily.

This incident illustrates the potentially catastrophic events that may occur when a PEEP valve is accidentally malpositioned. As it is currently designed, the inflow port of the PEEP valve has an external diameter of 22.4 mm. When the PEEP valve is reversed the inflow port can be connected to standard tubing having an internal diameter of 22 mm. This permits connection between the reversed valve and the endotracheal tube of the patient.

The manufacturer has attempted to obviate misconnection of the PEEP valve by use of labels on the inflow and outflow ports. However, these may be overlooked during an emergency as in the case just described. We feel that the safety of this PEEP valve can be enhanced by modification of the diameter of the connecting ports so that inadvertent misconnection cannot occur. In the meantime, vigilance is necessary to prevent improper attachment of the Vital Signs PEEP valve and Pulmanex bag.

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Use of Succinylcholine in Patients with Decreased Plasma Cholinesterase Activity

To the Editor:

I read with interest the recent review article by Gaines and Rees on anesthetic considerations in electroconvulsive therapy (1). They state that the use of succinylcholine is contraindicated in patients with decreased plasma cholinesterase activity. However, it has been documented that succinylcholine can be used quite successfully in this situation provided that an adjustment in the dose is made (2). When they studied a patient with atypical plasma cholin-

esterase who presented for a course of ECT, Cass et al. suggested a dose of 0.05–0.1 mg/kg (3).

Recently we studied a patient with documented atypical plasma cholinesterase presenting for ECT (4). We found that 0.04–0.06 mg/kg of succinylcholine produced 90% depression of first twitch height, which provided adequate neuromuscular blockade to facilitate ECT. This dose was compared with an equipotent dose of atracurium (0.23 mg/kg) followed by edrophonium and atropine. The time to 90% first twitch recovery was 20 min with succinylcholine and 16 min with atracurium. Thus, atracurium had no advantage over small doses of succinylcholine. The use of succinylcholine does not appear to be contraindicated in a patient with atypical plasma cholinesterase who presents for ECT provided that an appropriate dose is used.

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Epinephrine Reduces Systemic Absorption of Extradural Diacetylmorphine (Heroin)

To the Editor:

We read with interest the recent paper on the addition of epinephrine to extradural diacetylmorphine (heroin) by Jamous et al. (1). In a similar study on extradural diacetylmorphine analgesia after cesarean section (*Br J Anaesth*, in press) we obtained comparable results with respect to duration of analgesia. Using the same dose of extradural diacetylmorphine (5 mg) we also found that although duration of analgesia was not significantly prolonged (12.51 hr compared to 9.9 hr) by the addition of epinephrine (10 ml 1:200,000), the predictability of analgesia was significantly increased, with 77% of patients having more than 8 hr of good analgesia compared to only 48% with diacetylmorphine alone.

However, unlike Jamous et al, we found no significant reduction in diacetylmorphine absorption as measured by the area under the plasma morphine concentration time curve, although time to peak plasma morphine concentration was significantly delayed from 36 to 78 min by the addition of epinephrine. Our peak plasma morphine concentration (mean $\pm$ SEM) for diacetylmorphine alone was

18.27 ± 4.23 nmol/L at 38.8 ± 8.9 min compared with 14.73 ± 2.06 nmol/L at 78.3 ± 19.4 min for diacetylmorphine with epinephrine. These levels are markedly lower than those of Jamous et al., and also those of Watson et al. (2), both of whom used the same dose of diacetylmorphine. They are also much lower than the mean effective analgesic concentration of morphine, which has been quoted to be 53 nmol/L (3). The reason for our lower morphine concentrations may well lie in the nature of the assays used. The radioimmunoassay used by both Jamous et al. and Watson et al. may have detected not only morphine but also monoacetylmorphine, morphine-3-glucuronide and morphine-6-glucuronide, whereas the high pressure liquid chromatography assay (4) we have used is specific for morphine.

Like Jamous et al., we encountered no major adverse effects but were surprised to note a higher incidence of vomiting in patients given diacetylmorphine and epinephrine, with 29% vomiting when epinephrine was used compared to only 4% in patients given diacetylmorphine alone. We assumed this higher incidence of vomiting associated with epinephrine was due to a relatively higher dural transfer of diacetylmorphine, with enhanced drug levels in the spinal compartments, including CSF, and increased rostral spread in the CSF.

Notwithstanding the higher incidence of vomiting, we have found the benefits of more consistent prolonged analgesia outweigh the disadvantages of this side effect, and extradural diacetylmorphine with epinephrine is now routinely used to provide analgesia after cesarean section.

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Epidural Blood Patch in a Jehovah's Witness

To the Editor:

Jehovah's Witnesses pose special ethical, legal, and moral dilemmas in anesthesiology because of their refusal to accept transfusions of blood or blood products even in cir-

cumstances in which their lives may be at risk. Many Witnesses refuse transfusion of their own blood if it loses physical continuity with their circulation (1,2). There are no reports of how to solve this problem in a Jehovah's Witness who needs an epidural blood patch. We describe a novel technique of performing an epidural blood patch that was acceptable to a member of this sect because continuity with her circulating blood volume was maintained.

A 24-yr-old Jehovah's Witness developed a classic postdural puncture headache after spinal anesthesia for cesarean section. The headache failed to respond to conservative management for 4 days. After explanation of the procedure for epidural blood patching, she announced it would be unacceptable because the blood used would lose physical continuity with her circulation. To obviate this problem, we devised a simple apparatus that allowed us to perform the blood patch in a way that was compatible with her religious convictions.

With the patient in the right lateral position, a 17-gauge Tuohy needle was placed in the epidural space overlying the dural puncture. Using aseptic technique, a 16-gauge cannula was placed intravenously in the left arm. Two 50-cm IV extension tubes (Medex Inc., Hilliard, OH) were connected in series to the cannula. By attaching a three-way stopcock and syringe to the other end of the extension tubing, 20 ml of blood was drawn into the syringe, thus creating a continuous column of blood in direct continuity with her circulation. The stopcock was then attached to the hub of the Tuohy needle and the 20 ml of blood was slowly injected into the epidural space, giving almost immediate relief of her headache. After 2 hr of bed rest she felt completely better and went home. When seen 3 weeks later for follow-up she remained well and free of complications.

Continued cerebrospinal fluid leakage through a dural puncture is often incapacitating and occasionally serious (3-5). Epidural blood patching is a simple, safe, and effective procedure that, with our minor modification, is theologically acceptable to Jehovah's Witnesses.

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Improving Anesthesia Mask Fit in Edentulous Patients

To the Editor:

Airway management in edentulous patients is often made difficult by the anatomic variations that accompany the edentulous state. In addition to loss of teeth, these patients may suffer from wasting of the perioral tissues, atrophy of the maxillary and mandibular bones, and "compensatory" hypertrophy of the tongue (1,2).

Application of an anesthetic face mask in the conventional manner often results in poor mask-to-patient fit and loss of gas from the patient-anesthesia circuit unit. This airway leak most often occurs at the angle of the mouth—as was the case in the patient pictured in Figure 1—and is influenced by the loss of structures supporting the buccal folds in patients with normal dentition (2). Difficulty in airway management may be further exacerbated by the anesthetist's inability to protrude the patient's mandible and thus anteriorly displace the enlarged tongue.

Previous suggestions to improve mask fit in edentulous patients have included leaving dentures in place, inserting nasopharyngeal or oral airways, or packing the buccal areas with sponges. These techniques have the disadvantage that they may produce coughing, gagging, or bleeding, or may introduce an unsecured object into the airway.

A simple alternative method for improving mask fit in edentulous patients involves the use of commonly available equipment in an unusual fashion. Using a triangularly shaped anesthesia mask such as the SCRAM or Trimar (Inter-tech/Ohio; Bannockburn, IL), the patient's mouth is opened, and the inferior, horizontal border of the mask is placed between the gingiva of the maxilla and mandible (Figure 1A). With the patient's mouth closed on this mask border, the mask is rotated onto the face so that the superior angle conforms to the nose (Figure 1B). Rotation of the mask onto the face uses the inferior margin of the mask as a fulcrum upon which the mandible may be protruded. The curved, lateral borders of the mask now conform to the curved facial surfaces overlying the maxilla.

Choice of mask size is of critical importance when using the modified mask placement. Most patients require a mask that is one size smaller than that used in conventional management of the mask airway. Choosing a mask that is too large will merely shift the airway leak from the angle of the mouth with the conventional mask placement to the nasion when using the modified mask placement.

The advantage of using the described technique to improve mask fit is that it uses readily available equipment, it does not introduce unsecured foreign bodies into the airway, and it does not cause coughing, gagging, or bleeding. Furthermore, the technique may be initiated in either awake or anesthetized individuals.

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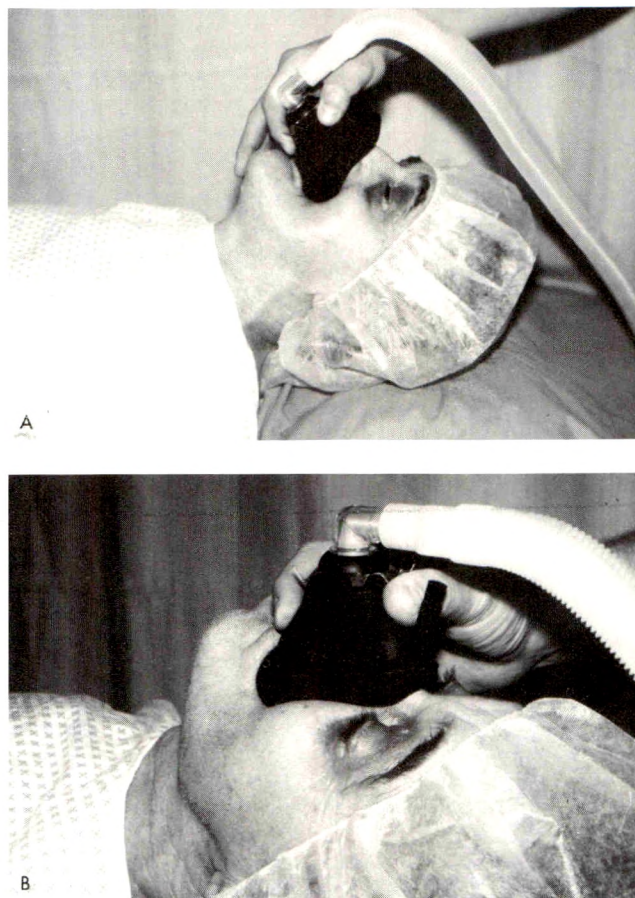


Figure 1. Modified method of anesthesia mask placement in an edentulous patient. (A) After the inferior margin of the mask is placed between the maxillary and mandibular gingiva, the mouth is closed. (B) Mandibular protrusion occurs as the superior angle of the mask is rotated posteriorly to form a seal between the mask and the maxillary and nasal surfaces of the face.

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Seizures after Anesthesia: Identifying the Causes

To the Editor:

The clinical report by Harrison concluded that occurrence of myoclonic type movements of the shoulders and arms of a patient in the recovery room after a nitrous oxide-isoflurane anesthetic supported the possibility that isoflurane may act as a rare but possible cause of seizurelike activity (1).

Harrison compares her case to that reported by Hymes (2) in that abnormal movements occurred and persisted after discontinuation of anesthesia. However, withdrawal phenomena have been observed in clinical situations immediately after cessation of 30% nitrous oxide anesthesia (3). These consisted of diffusely distributed paroxysmal bursts of high voltage θ (4-7 Hz) activity. Frank convulsive activity has been induced in mice after removal from a 4-15 min exposure to 1.45 atmospheres of nitrous oxide in air in a hyperbaric chamber (4). This response has been likened to the spasms seen when chronic alcohol administration is discontinued and suggests that the withdrawal convulsions might have some clinical parallels such as delirium or excitement during recovery from anesthesia. The threshold for inducing convulsive activity was decreased in a cat model. Discontinuation of nitrous oxide produced status epilepticus in one animal. Also, abnormal muscle movements have been observed during administration of the gas. Volunteers exposed to 1-5 atmospheres nitrous oxide exhibited tachycardia, hypertension, muscle rigidity, jerking movements and even opisthotonus. A few subjects had hyperactivity alternating with apparent relaxation (5). Indeed one case report associated clinical nitrous oxide administration with frank convulsions (6).

Thus, in searching for a cause of myoclonic activity after isoflurane-nitrous oxide anesthesia, nitrous oxide rather than isoflurane may be the cause.

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In Response:

There have indeed been reports of EEG changes (1), involuntary twitching in dogs (2), and even frank convulsions in mice after nitrous oxide withdrawal (3); however, the two studies reporting the occurrence of involuntary movements and convulsions used nitrous oxide at 1.45 and 1.7 atm. Hornbein et al. reported muscle rigidity, jerking movements, and a few instances of hyperactivity alternating with apparent relaxation occurring at 1.5 atm nitrous oxide, but disappearing at 1.1 atm. (4).

In the clinical situation described, the patient had not

received hyperbaric nitrous oxide. Although nitrous oxide cannot be completely ruled out as a possible etiologic agent, isoflurane as the primary anesthetic is still implicated as a rare but possible cause of seizure activity as described in the reported case.

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Nitrous Oxide Should Not Be Used during Laser Endoscopic Surgery

To the Editor:

In their recent report on anesthesia for CO₂ laser surgery, North et al. (1) used 50% nitrous oxide and 50% oxygen with isoflurane for maintenance of anesthesia. This mixture needlessly exposed their patient to the risk of fire or explosion.

Although nitrous oxide is non-flammable, it supports combustion (2). Gaba et al. (3), for example, showed that mixtures of nitrous oxide and oxygen support the combustion of endotracheal tubes ignited by a CO₂ laser just as readily as 100% oxygen does. They and others (4) recommend that the minimum clinically acceptable concentration of oxygen be used along with nitrogen or helium during laser surgery in the airway.

Fried (5) showed in a recent survey that endotracheal explosion was the most common serious complication of CO₂ laser laryngologic surgery. Accounts of such incidents have been widely published. The elimination of nitrous oxide from the anesthetic gases should decrease the frequency of these catastrophes.

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In Response:

We certainly agree with Dr. Sosis that ignition of tracheal tubes during CO₂ laser surgery is most undesirable. We are also aware that nitrous oxide supports combustion just as well as oxygen (1,2).

The laser is an intense heat source capable of igniting many materials. The case with which this occurs depends on the material itself, the gas environment surrounding the material, and the focus of the laser beam.

In our case, we chose to protect the external surface of a vinyl plastic tube with copper tape, and we chose to limit the oxygen and nitrous oxide concentrations in the region of the lesion, the larynx, by using a cuffed tracheal tube. The gas surrounding our tube in the region exposed to the laser was room air.

An understanding of how and why our tubes ignite, not the elimination of certain gases, will decrease the frequency of tube ignition during CO₂ laser surgery.

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Delayed Filling of the Breathing Bag due to a Portable Vaporizer

To the Editor:

During the preanesthetic check of an anesthesia machine (Ohio Serial No. ABDD 00197), we noticed that the breathing bag was taking longer (8 sec) than expected to fill when oxygen flush was initiated. We also heard the sound of a gas leak from the pressure relief valve located under the anesthesia machine's table top. Because the pressure relief valve is set at 140 cm H₂O, such a leak signified an excessive pressure buildup in the anesthesia circuit beyond the pressure relief valve. The machine was checked for kinks or blocks in the tubings, circuits, soda lime, and connectors, but no kinks or blocks were found.

We next tested another machine of similar design. It took less time (5 sec) to fill the breathing bag under the same conditions as that of the previous machine (i.e., time taken to fill the breathing bag up to 40 cm H₂O pressure, once the oxygen flush device was activated and the Y-connector

of the anesthesia circle system was occluded with no flow from the flow meter). We could not detect any gas leaks from the pressure relief valve. The only difference between the two machines was that the machine in which the breathing bag filled slowly included a portable Fortec vaporizer (Cyprane) between the fresh gas flow outlet of the anesthesia machine and the soda lime canister. We placed another vaporizer of the same design in the second machine between the fresh gas flow outlet and soda lime canister and then tested the machine for gas leaks; we observed the same slow filling of the breathing bag that we did in the first machine.

With the help of the Ohio machine sales representative, we discovered that when the portable vaporizer (Cyprane-Fortec) was included in the anesthesia circuit beyond the pressure relief valve, when the vaporizer is in the off position, and when the oxygen flush is activated, the bypass circuit of the Cyprane vaporizer generates pressure greater than 140 cm H₂O, thus opening the pressure relief valve. This phenomenon causes loss of gases into the atmosphere through the pressure relief valve, thus delaying the filling of the breathing bag. Slow filling of the anesthesia breathing bag may be undesirable in an emergency situation and may distract the anesthetist from the care of the patient even in the absence of an emergency.

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Detection of Systemic to Pulmonary Shunt by End-Tidal Carbon Dioxide Concentration

To the Editor:

The ability to continuously measure the expired CO₂ of patients permits monitoring of such vital functions as metabolic rate, ventilation, and pulmonary perfusion (1). We recently observed an infant in whom the end-tidal carbon dioxide tension (PETCO₂) led us to search for a systemic to pulmonary shunt after establishing cardiopulmonary bypass.

A 2-day-old, 4.2 kg baby girl with total anomalous pulmonary venous return was scheduled for total cardiac repair. Cineangiograms obtained during right heart catheterization had shown the pulmonary veins draining into the coronary sinus. Anesthesia was induced and maintained with fentanyl and muscle relaxation established with pancuronium. One hundred percent oxygen was administered via a preexisting endotracheal tube and respiratory support maintained with a Servo Ventilator 900C (Siemens-Elema AB, Ventilator Division, Sweden). Monitoring included an umbilical arterial pressure line, intermittent measurement

of arterial blood gas tensions, pulse oximetry, and continuous measurement of PET_{CO_2} (CO_2 analyzer 930, Siemens-Elema AB). End-tidal CO_2 concentration prior to cardiopulmonary bypass was 3.8–4.1% (28–32 mm Hg). After the heart was surgically exposed, the aorta was cannulated and a single venous return cannula was placed into the right atrium. Upon establishing cardiopulmonary bypass, the mean arterial pressure fluctuated between 35–39 mm Hg. The PET_{CO_2} decreased from 3.9% to 2.1% rather than to the 0.5% or less usually observed during cardiopulmonary bypass. The pulmonary artery did not appear distended and venous drainage to the membrane oxygenator appeared adequate. Because the PET_{CO_2} remained elevated, suggesting significant blood flow through the pulmonary vessels, the great vessels were explored for a patent ductus arteriosus. When the ductus arteriosus was located and temporarily clamped, the PET_{CO_2} decreased to 0.27% and the mean arterial pressure increased to 50 mm Hg. Upon release of the clamp the PET_{CO_2} increased to more than 2% and the mean arterial pressure decreased. The ductus was securely ligated, the PET_{CO_2} decreased to less than 0.2%, and the mean arterial pressure increased and remained stable. The procedure continued without incident.

The PET_{CO_2} closely reflects the PCO_2 of mixed venous blood (2). If alveoli are not perfused, as in pulmonary embolism, the PET_{CO_2} decreases (3). During cardiopulmonary bypass in small infants, blood flow is diverted away from the pulmonary circulation by a single venous cannula draining the right atrium and, consequently, PET_{CO_2} decreases. In our patient, however, the PET_{CO_2} monitor showed a PET_{CO_2} well above 0.5% indicating that the pulmonary vascular bed was probably still being perfused. This prompted us to search for a systemic to pulmonary shunt. In most instances, such a shunt would be detected during cardiopulmonary bypass by distention of the pulmonary artery and the left side of the heart. Such distention did not occur because the pulmonary veins emptied into the coronary sinus, which drained into the right atrium where the single venous cannula was located. The elevated PET_{CO_2} and the low mean arterial pressure indicated that the pulmonary blood flow had not ceased and that blood was being shunted away from the systemic circulation. These events would be consistent with a patent ductus arteriosus or other systemic to pulmonary shunt. The rapid decrease in PET_{CO_2} and the increase in the mean arterial pressure after the ligation of the ductus confirmed our clinical diagnosis.

In summary, in patients where pulmonary venous to right atrial communication exists, as in our patient or patients with transposition of the great vessels with patent foramen ovale, the PET_{CO_2} can be used to detect pulmonary blood flow during cardiopulmonary bypass. We suggest that not only in these patients, but also in other selected patients with congenital heart disease, measurement of PET_{CO_2} is a useful monitoring device to detect systemic to pulmonary shunts.

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A Hitherto Unreported Virtue of the Isolated Power System

To the Editor:

The organizations whose leadership masterminded revision of the electrical code to allow grounded power in the operating room are composed of individuals most of whom rarely visit the surgical suite while operations are in progress. They fault the previously required isolated (ungrounded) power system (IPS) for failure to protect that small group of patients who have been rendered vulnerable to "microshock" and hence require special precautions. Ignored is the fact that the overwhelming majority of patients, as well as operating room (OR) personnel, are safer when their often wet environment includes an isolated system that alarms with a hazard current of 5 mA rather than a grounded system poised to deliver ground-seeking currents three orders of magnitude higher.

Caring for patients undergoing surgery in facilities still equipped with IPS allows us daily observation of this purported anachronism. We wish to draw attention to an advantage of the system that has not, to our knowledge, been reported.

Surgical nurses were preparing one of our ORs for the first case of the day. As part of this preparation, the steam sterilizer located in the OR was loaded and energized.

Upon returning from their morning conference, the nurses found the line isolation monitor (LIM) for their OR sounding an alarm. They reported this to the appropriate anesthesiologist. He noted that the LIM meter indicating hazard current was off scale, this predictive value exceeding 3 mA. The audible alarm was then silenced, and all movable electrical apparatus in the OR was unplugged. Noting no effect upon the meter reading, the anesthesiologist concluded that the problem lay in permanently installed equipment.

The patient scheduled for the affected OR was taken instead to an adjacent room and the maintenance department notified of the problem. Finally, 15 min or more after the LIM signal was discovered, a "low temperature" alarm sounded on the autoclave . . . the first indication from that instrument of a malfunction.

Investigation revealed that a jet of steam from a leaky coupling was spewing over a solenoid in the autoclave, thereby establishing an aberrant electrical pathway between power line and ground sufficient to be detected by the LIM.

Opponents of isolated power in the OR have argued that "nuisance alarms" plague the system. This allegation was a factor in the successful drive to elevate the LIM alarm level from 2 to 5 mA of hazard current. Strangely, such alarms have not proved a problem in our surgical suite despite utilization of LIMs set to the more stringent 2-mA standard. Thus the anesthesiologist did not dismiss this signal as just a "nuisance" but instead took appropriate action.

In addition to its virtues relating to patient and personnel electrical safety plus continuity of power under some fault conditions, the IPS in this case offered the advantage of providing distant early warning (DEW) of a steam leak.

The importance of a signal from the LIM must be kept in perspective, however. The etiology of a LIM alarm may range from high impedance leakage (as in this case) to a dead short-circuit line-to-ground (worst case fault), but even under worst-case alarm conditions, isolated power can never pose an inherent hazard greater than that *continuously* present with grounded power. The latter has now been made permissible in the OR.

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Preoxygenation and Electroconvulsive Therapy

To the Editor:

In their review article on anesthesia for electroconvulsive therapy (ECT), Gaines and Rees (1) suggested that preoxygenation of distressed patients may be safely omitted. I, too, believed that application of a face mask may increase anxiety in psychiatric patients and in my practice did not preoxygenate. However, the advent of portable, noninvasive pulse oximeters has allowed study of arterial oxygen saturation (SaO_2) of patients before and during ECT treatments. In a pilot study, the finger probe of a Biox 3700 pulse oximeter (Ohmeda, Boulder, CO) was attached to each patient while inspiring room air. Arterial oxygen saturation was continually monitored while a solo anesthesiologist conducted the general anesthetic. Anesthesia was induced with methohexital (IV), and succinylcholine was administered. Manual ventilation with a face mask using 100% oxygen commenced immediately after loss of consciousness. After unilateral ECT, each patient made an uneventful recovery. The SaO_2 values shown in Table 1 are: 1) recorded while breathing room air; 2) the lowest value observed during the induction period; and 3) the highest value observed during anesthesia.

Because several low postinduction values were recorded, the study was discontinued. Our data support an earlier study that found arterial desaturation not uncommon during tracheal intubation when preoxygenation is omitted (2).

Table 1. SaO_2 Values in Four Patients Undergoing Electroconvulsive Therapy

Patient age (yr)	Room air SaO_2 (%)	Postinduction minimum SaO_2 (%)	Postinduction maximum SaO_2 (%)
61	95	85	100
73	96	89	99
35	99	97	100
66	98	90	100

My practice now includes routine preoxygenation of patients presenting for ECT. After adequate explanation, psychiatric patients generally cooperate with this practice. Many patients appear relaxed while "holding their own" face mask before induction of anesthesia (3).

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A Breathing-Circuit Stethoscope for Continuous Monitoring of Breath Sounds

To the Editor:

Precordial and/or esophageal stethoscopes have been widely used to monitor breath and heart sounds during anesthesia. However, a precordial stethoscope cannot be used during thoracic surgery, and often does not provide reliable breath sounds in obese patients. An esophageal stethoscope may cause nasal or oral bleeding, especially in patients with bleeding tendencies, and may be difficult to insert when a nasogastric tube has already been placed. Additionally, accidental tracheal misplacement of an esophageal stethoscope may lead to hypoxemia (1).

We developed a breathing-circuit stethoscope that is noninvasive and can provide breath sounds of excellent quality and quantity. The apparatus consists of a 45-cm length of a 16-French polyvinyl chloride (PVC) catheter and a transparent plastic tube that can be interposed between the corrugated tubing and the Y-connector (Fig. 1). The portion of the PVC catheter to be placed in the breathing tube is sealed at one end, with multiple perforations 3 cm from the tip, and then covered with a low pressure balloon similar to that used in an ordinary esophageal stethoscope. The plastic breathing tube is pierced with a hole of 3 mm

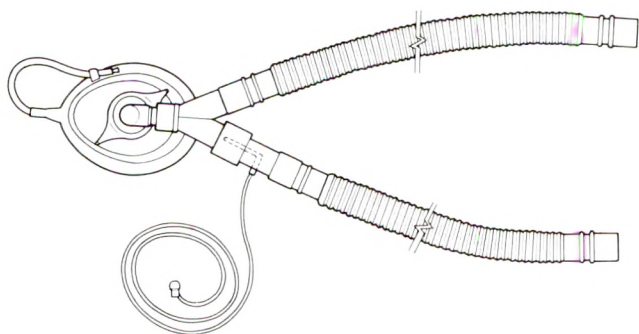


Figure 1. Diagram of a breathing-circuit stethoscope interposed between corrugated tubing and a Y-connector.

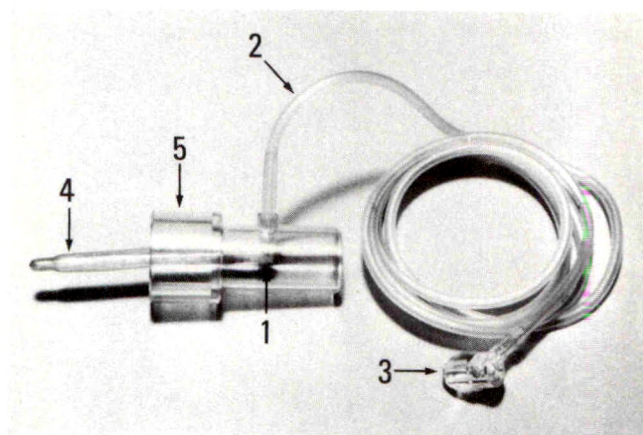


Figure 2. Closeup of a breathing-circuit stethoscope. 1) Right angle metal tube; 2) PVC catheter; 3) ear-piece; 4) cuff on end of PVC catheter; 5) breathing tube.

diameter through which the distal 5-cm portion of the PVC catheter is inserted. The soft balloon covering the distal portion of the PVC catheter is horizontally fixed in the mid-position of the plastic tube by a rigid small-caliber plastic pipe, 3 mm external diameter, also passed through the hole in the breathing tube. The PVC catheter passes through this rigid 90° angled pipe and is connected with a monaural earpiece in the proximal portion (Fig. 2).

Advantages of the breathing circuit stethoscope include, first, the ability to detect the presence of intratracheal retention of secretions and to do so more rapidly than with precordial or esophageal stethoscopes because breath sounds of sufficient quantity and distinct quality are carried directly to the anesthetist's ear through the patient's trachea and bronchi. Second, this technique is completely noninvasive and therefore complications associated with insertion of the esophageal stethoscope can be avoided. Third, the stethoscope can be easily attached to any breathing circuit at any time, whether the patient is intubated or anesthesia is maintained by mask, regardless of age and concurrent illness. Finally, the breathing-circuit stethoscope costs less than the esophageal stethoscope because it can be sterilized and repeatedly used.

There are also disadvantages to the breathing-circuit

stethoscope. One is the inability to detect endobronchial intubation. Another is that although heart sounds can be heard, they are more clearly heard with the esophageal stethoscope. The breathing-circuit stethoscope cannot substitute completely for the precordial stethoscope or the esophageal stethoscope. We think that different types of stethoscopes should be available and used as conditions require. We believe that the addition of this apparatus to the conventional stethoscopes will prove valuable in monitoring patients' airways more noninvasively.

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Radial Arterial Foreign Body as a Cause of Wrist Pain

To the Editor:

Wrist pain, a common orthopedic complaint, has many causes. When pain is reported in the anatomical snuff-box after catheterization of the radial artery at the wrist, the possibility of a broken fragment of the catheter embolizing to the snuff-box must be considered. The following is a report of such a case.

A 72-yr-old man undergoing aortofemoral bypass surgery had a plastic arterial catheter inserted into the right radial artery. The catheter was removed after 48 hr and the patient was discharged 2 weeks later after an uneventful recovery. The catheter was apparently not examined after removal.

Two weeks after discharge, the patient was seen in the orthopedic clinic with a complaint of right wrist pain. He stated that starting approximately 4 days after discharge, he had increasing pain in the region of the right anatomical snuff-box. He denied any history of trauma and was unaware of any previous joint disease.

On examination there was tenderness in the anatomical snuff-box with slight erythema and swelling but no fluctuation. Radial and ulnar deviation of the wrist was painful but volar and dorsiflexion were not. The radial pulse was palpable and there was adequate circulation to the hand. X-ray films (Fig. 1) revealed a small erosion in the region of the scaphoid and an overlying foreign body suggestive of a piece of plastic tubing. A xeroradiograph confirmed this impression (Fig. 2). The patient was taken to the operating room and under regional anesthesia, a 1-cm fragment of plastic catheter was found within the lumen of the radial artery. The fragment was removed and the vessel repaired with a 7-0 nylon suture. The patient was followed up in the clinic. When he was last seen, approximately 1



Figure 1. X-ray film of the wrist showing a piece of plastic catheter in the region of the anatomical snuff box.

yr after surgery, his wrist was asymptomatic. An Allen test at that time (1 yr after injury) indicated good flow through the radial artery of the right wrist but sluggish flow through the ulnar artery. Doppler sonography confirmed this impression and provided additional evidence of patency of the radial artery in the snuff-box. The cause of diminished ulnar arterial flow was not investigated.

Complications associated with radial artery catheterization, although reported extensively (1-7), have not included embolization of an intraarterial catheter to the anatomical snuff-box with subsequent presentation as a painful wrist. The anesthesiologist should be aware that a complication of this nature may later present to the orthopedic or hand surgeon. The appearance on x-ray of an erosion in the scaphoid in the vicinity of the foreign body in our case is without explanation. Hyperemia secondary to inflammation in the region of the foreign body is a possibility, but a long-standing change due to unrelated causes is equally likely.

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Figure 2. Xeroradiogram of the same wrist showing the foreign body.

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Removal of Endotracheal Tube Connectors

To the Editor:

We have developed a quick, easy, and safe method for removing plastic connectors from endotracheal tubes. Impetus for this report comes from an incident that occurred in an intensive care unit.

A 54-yr-old man who was recovering from aortic bi-

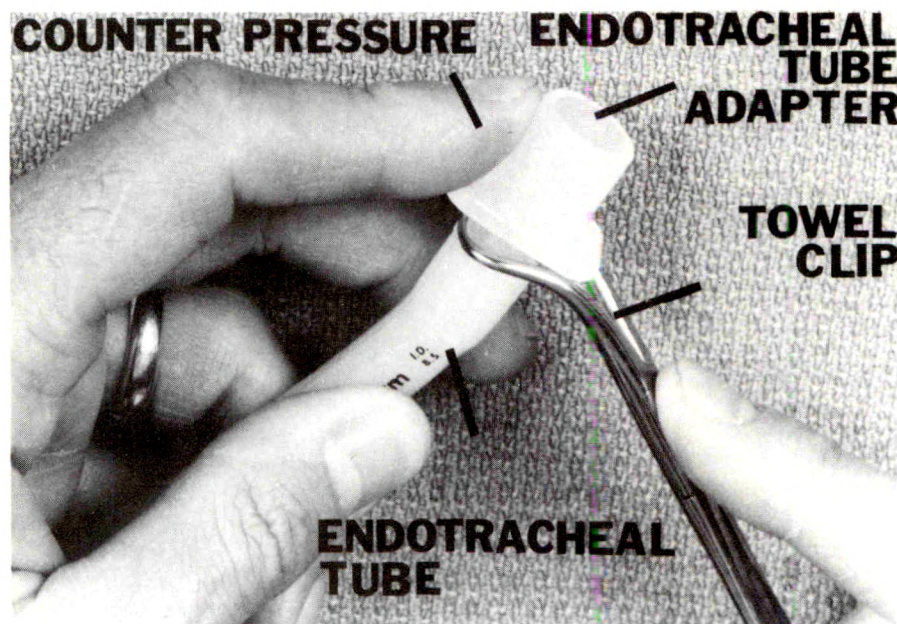


Figure 1. Technique for separating endotracheal tube connectors from tubes using a towel clip and counter pressure.

femoral bypass surgery was immobilized, sedated, and mechanically ventilated when tracheal suctioning was required. When the nursing staff was unable to separate the ventilator from the plastic endotracheal tube connector, assistance was sought from a surgeon caring for the patient. Because traction on the plastic connector tended to tighten the press fit between it and the endotracheal tube (similar to the action of a Chinese finger trap), the surgeon cut the tube below the level of the connector. However, after tracheal suctioning, he was unable to remove the small tube segment still attached to the connector and therefore could not reconnect the ventilator. As a result, the patient was not ventilated for several minutes while a new endotracheal connector was obtained. An emergency call for anesthesia personnel was made, and when help arrived the patient was noted to be cyanotic and in respiratory distress. Using the technique described below, the problem was quickly solved and mechanical ventilation restored.

Figure 1 shows our technique, in which a towel clip is applied circumferentially to the base of an endotracheal tube connector. The "shoulder" of the metal clip functions as a fulcrum against the under surface of the flange of the connector, and the closed points of the clip act as a lever to

push the two components apart. At the same time, mild counter pressure is applied to the larger, open end of the connector. We have found that this technique works best for endotracheal tubes with diameters greater than 4 mm. Similarly, a towel clip also may be used to separate a tight fitting plastic elbow connector "frozen" to an endotracheal tube connector.

This technique will be of interest and value to most anesthesiologists (who are aware of the hazard of cutting an endotracheal tube after placement in a patient's airway), as well as to intensive care personnel when confronted with an endotracheal tube connector that is "frozen" in an endotracheal tube or an elbow tightly pressed to the larger (22 mm) end of the endotracheal tube connector.

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Book Reviews

The Psychological Experience of Surgery

Richard S. Blacher, ed.

New York: John Wiley & Sons, 1987, 236 pp, \$31.50.

Life without memory is no life at all. . . Our memory is our coherence, our reason, our feeling, even our action.
Without it we are nothing. . .

—Luis Bunuel

The fields of anesthesiology and psychiatry have a great deal in common. The purpose of both is the diminution of the patient's experience of pain through pharmacological or psychological intervention at the level of the central nervous system. Both fields work intimately with memory. The goal of the psychiatrist is to restore and restructure memories where they have been repressed and distorted as a result of psychological conflict. The process is aimed at the reestablishment of psychological equilibrium. The anesthesiologist works to abolish the experience of pain via amnesia and analgesia. It is not often that the anesthesiologist conceives of his job in terms of the restoration and restructuring of memory. The understanding of the emotional and psychological background of surgical illness as offered in this book allows the anesthesiologist to see his limited contact with the patient in terms of the bigger picture.

Dr. Richard Blacher is a consultation/liaison psychiatrist who for many years has been making important contributions to the understanding of the psychiatric aspects of medical illness. His focus has been on the patient's experience of surgery in all of its depth and complexity. His work on the diagnosis and management of patients who have suffered awareness during anesthesia is classic (1,2).

In this very important volume, Dr. Blacher presents an engaging and enlightening account of the patient's experience of surgery. Each chapter focuses on a different variety of surgical illness. Issues of psychological meaning are explored in depth. Rather than presenting purely hypothetical constructs, the authors give the reader actual case examples that illustrate the salient points. Topics covered include the emotional response to the experience of surgery and anesthesia, pediatric surgery, cardiac, breast, gynecologic, cancer, burn, intestinal bypass, and cosmetic operations. Also discussed are neurosurgery, amputations, transplantation, and psychotherapeutic intervention for surgical patients.

Despite being a multiauthored work, this volume exhibits a uniformity of style as clear evidence of the editor's hand in its preparation.

The importance of this book rests in what it has to offer

the anesthesiologist and surgeon. Much of what is written here is common knowledge to the psychiatrist. What is to be learned and reinforced here is that our patients have a past, and they have a future. The process of surgery and anesthesia is a part of that history. To the extent that we understand that, and with the help of Dr. Blacher and his colleagues, our patients can be best served.

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References

1. Blacher RS. On awakening paralyzed during surgery: a syndrome of traumatic neurosis. *JAMA* 1975; 243: 67.
2. Blacher RS. Awareness during surgery (editorial). *Anesthesiology* 1984; 61:1.

Anesthesia and Neurosurgery

James E. Cottrell and Herman Turndorf, eds. St. Louis: CV Mosby, 1986, 530 pp, \$75.00.

The editors state in the Preface that the aim of this book is to "provide the essential scientific basis for a rational approach to clinical neuroanesthesia." In fact, the book is a reasonable but uneven effort to achieve this ambitious goal.

One strength of this multiauthored text is the list of contributors. Many of the chapters are written by knowledgeable basic scientists and experienced clinicians. Most of the clinical chapters are comprehensive and solid, if not always inspiring or imaginative, and the basic science is good. Perhaps the most significant improvement in the book is that it now covers important areas that were neglected in the first edition. New chapters on pediatric neuroanesthesia, patients with neuroendocrine disease, aneurysms, carotid surgery, pain, and complications in neuroanesthesia have been added and the chapter on neurophysiologic monitoring has been expanded. These chapters give the book needed clinical depth and breadth.

There are also significant weaknesses. Some chapters have not been revised or updated adequately. The chapter on cerebral and spinal cord blood flow, for example, devotes more space to methoxyflurane and cyclopropane than to isoflurane (which shares six lines with enflurane) and the most recent references are from the late 1970s. The chapters on neuroradiologic procedures deal in depth with pneu-

moencephalography but only briefly address anesthesia for magnetic resonance imaging. Repetition, particularly of the basic concepts of cerebral blood flow and intracranial pressure, is excessive. Some chapters contain good basic science material but tend to neglect clinical application. The chapter on intracranial pressure, for instance, contains an inordinate amount of information on historical development and complicated data analysis but does not adequately address indications for ICP monitoring or evidence that treating high ICP improves outcome. Similarly, the chapter on cerebrospinal fluid mechanisms describes CSF production and excretion in detail but does not mention anesthetic effects on these processes. It is puzzling why certain chapters were included at all. A lengthy chapter on "brain states" is scholarly, but completely out of place in a text of this nature. The chapter on free-radical mechanisms of CNS injury is undoubtedly authoritative and complete but, considering that the hypothesis is not proven, it is also inappropriately specific for a general neuroanesthesia text.

There is good information in this book, but because of unevenness in content, it is not a text one reads cover to cover. In fact, the book is perhaps best viewed as a reasonably up-to-date, comprehensive resource (including an extensive reference list) to be consulted when specific questions arise on certain basic and clinical aspects of neuroanesthesia. Thus, we believe this is probably not a "must own" book for residents or the occasional neuroanesthesia practitioner but that it should be available in departmental and hospital libraries.

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Drug Interaction in Anesthesia

N. Ty Smith and Aldo N. Corbascio, eds. Philadelphia: Lea & Febiger, 1986, 482 pp, \$47.50.

Here is yet another text relating drug interactions to anesthesia, and a welcome addition it is. This is the second edition of this text, the first having been published in 1981. This new edition has five additional chapters, more extensive coverage of pharmacokinetics, and updated information that has been reported and confirmed in the 5-year interval since the first edition was published.

The list of authors includes 39 prominent, experienced clinicians and pharmacologists, of whom only 2 are not physicians. Their combined efforts have produced 27 chapters in this fine textbook.

The introductory chapter presents philosophical opinions and cautions from the senior editor. This is followed by a very brief (4 pages) "chapter" entitled "The Pre-Operative Visit"—a topic that warrants more ink and space

than many others. The third through the sixth chapters include excellent discussions of pharmacokinetics, including most of the advanced knowledge gained in this area during the last 5 to 6 years. The remaining 19 chapters present drug interactions with each chapter devoted to a particular class of drugs, e.g., Sympathomimetic Drugs, Antihypertensives, and Alpha Blockers, Inorganic Cations, etc. Each chapter contains clear, concise descriptions of the biochemical, pharmacologic, and physiologic interactions of a particular class of drugs with other drugs and with anesthetics. This is not a simple listing or compendium but, rather, a logical, easily understood discussion.

The clinical applicability of the description of each class of drugs is illustrated with one or two clinical case reports. The orientation is basically a clinical one, and is more or less complete. Scattered throughout the text, there are occasional opinions of the authors interspersed with the facts. Although these opinions are not universally shared, for example, on page 413, where Dr. David Cullen describes the depth of Anesthesia as being "just right" if "the patient does not move in response to incision, but rather shows reflex awareness that a painful stimulus has been applied", they do provide color and focal points for discussion. The readability of this text is uniformly excellent, in spite of the multiplicity of authors. This, plus the apparent consistency of style are a credit to the editorial functions of Drs. Smith and Corbascio.

Each chapter includes an ample presentation of figures, graphs, and tables to support the scientific bases on which the discussions are based. In addition, each chapter has its own very extensive bibliography. Further, the Index is very complete, occupying 43 pages (9%) of the book. It is detailed, specific, and generally inclusive, thus facilitating the use of the book as a reference.

This new addition to the Anesthesia literature will be well received. It will be of value to medical students in general, residents in Anesthesia, and to practicing physicians, especially anesthesiologists. Its value is not only as a text but as a reference source. It should be included in hospital libraries, and especially in those libraries maintaining and supporting teaching programs.

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Epidemiology in Anaesthesia: The Techniques of Epidemiology Applied to Anaesthetic Practice

J. N. Lunn, ed. Baltimore: Edward Arnold Ltd, 1986, 174 pp, \$34.50.

Principles and Practice of Research: Strategies for Surgical Investigators

H. Troidl, W. O. Spitzer, B. McPeck, D. S. Mulder, M. F. McKneally, eds. New York: Springer-Verlag, 1986, 380 pp, \$58.00.

A growing concern for risk management is focusing greater interest on studying adverse patient outcomes related to anesthesia care. We know much about the risks posed by anesthesia but little that is substantive and meaningful about patient outcomes following anesthesia. Two important books have appeared that should help fill this void.

Epidemiology in Anaesthesia is a deceptively small book that introduces the population-based study of disease (including mortality and complications) and its applications in anesthesia. Its editor is an anesthesiologist who has conducted the recent major British studies of patient outcomes after anesthesia. Several chapters present in clear, non-technical language the often confusing epidemiologic concepts of incidence and prevalence rates, sampling strategies and sample size determination, research designs, and reliability and validity testing of observations. John Bunker provides a historical perspective to the study of patient outcome in anesthesia. A particularly detailed chapter by Stephanie Duberman and Henrik Bendixen reviews recent studies of anesthetic-related mortality, morbidity, and risk, and provides guidance in avoiding their shortcomings in future studies. There are also similarly critical, chapter-length reviews of the anesthetic trace-gas and halothane-hepatitis controversies. Other chapters discuss the role of the anesthesiologist in the development of new drugs and in identifying adverse effects, and the development of the anesthetic record. Helpful line drawings and tables accompany the text, and the references are carefully chosen.

Principles and Practice of Research is a veritable vade mecum on surgical (and anesthesia) research, which is defined in this book to be mostly clinical research, with lesser attention devoted to animal studies and health services research. Its editors and contributors are prominent academicians in surgery, clinical epidemiology, statistics, and anesthesia in Western Europe, Canada, and the United States. In some 40 brief but meaty, well-planned and operationally oriented chapters, they offer guidance on all aspects of the topic, including evaluating previous work, critiquing the literature, planning and organizing a study, and evaluating the results. Sprinkled through the book are chapters devoted to ethics in clinical research, multicenter clinical trials, outcome measures, statistical methods, and the use of computers; appendices present the Declaration of Helsinki and guidance on animal care. The book is money well-spent if only to read Walter Spitzer's "Ten Tips on Preparing Research Proposals" and Sharon Wood-Dauphinee and Hans Troidl's "Endpoints for Clinical Studies: Conventional and Innovative Variables." One-fifth of the book is devoted to reporting research results in a variety of formats, from written abstracts and 10-minute presentations, to longer talks, poster sessions, and book chapters. Individual chapters also review the diversity and commonality of surgical research in nine countries. Quite appropriately, the book ends with a look to the future by Francis Moore.

Although both books should help anesthesiologists learn more about the study of adverse outcomes, the Troidl book is particularly well-suited to those in training and embarking on their first studies. Neither book, however, is designed as a self-contained guide but rather to alert the reader to many of the critical issues.

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Anesthesia and the Geriatric Patient,
Vol. 4, No. 4, October 1986 of the Clinics in
Anesthesiology. Philadelphia: WB Saunders, 1986,
1050 pp.

The past few years have seen the sudden appearance of several books concerning anesthesia and surgery in the elderly patient. In an intellectual climate where none had existed before, this sudden output parallels the awakening in our collective consciousness of the awareness of the rapid emergence of the elderly as an important clinical "subgroup". Their numbers and our interest in them have grown out of proportion to the body of scientifically verifiable "hard data" specifically pertaining to anesthesia that is available as an information base. Volumes upon volumes of fascinating information exist about the aging process, associated changes in physiologic functions, theories of aging, and pharmacology for the elderly patient. Little is available, however, in an organized format that specifically details imperatives for anesthetic management.

This paradox, plus the problems of a multiauthored volume in the format of a journal-type series, create a problem in full appreciation of the role for *Anesthesia of the Geriatric Patient* (Clinics in Anesthesiology) as a contribution to this growing mass of publications concerning anesthetic care of the elderly patient. Because this volume is basically a series of selected review articles without an organized transitional format from subject to subject, we are dependent upon the editor's judgement for topic selection. The authors represent a wide variety of backgrounds and writing styles that match the broad range of subjects. All of the subjects are appropriate and omissions of important aspects of surgical care for the elderly (pharmacology, urologic surgery, surgical risk, critical care, etc.) must be accepted as an expression of editorial bias, which is appropriate considering the length and format of this volume.

The chapters range in style from useful and practical "how to do it" (Outpatient Anesthesia, Orthopedics, Vascular, Ophthalmology) to academic (Thermoregulation, Respiratory Considerations, Diabetes, Nervous System, Cranial Vascular Surgery). Particularly provocative and challenging are the lessons to be learned by all of us from the chapter on Thermoregulation. This is an elegant and complete discussion of an often overlooked primary concern in anesthetic management of the elderly. The section on Diabetes comprehensively analyzes a vital subject that is often confusing to practicing anesthesiologists. The material on respiration is complete as well as clinically helpful. The discussion of outpatient management is instructive as all of us work to adjust to the need to develop less expensive aspects of good clinical care. An index partly unifies the broad range of subjects. A book like this truly is the sum of its parts and the editor has succeeded in presenting an instructive sampling of what we need to concentrate on if

we are to expand our ability to care for larger numbers of elderly surgical patients. There are many practical lessons that can be carried directly from a rapid scanning of the book to the OR. There are also many sophisticated points that will enhance our understanding of the elderly patient who needs to be anesthetized.

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Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Brown BB Jr, Copeland JG, eds. Anesthesia and Transplantation Surgery. Volume 10 in Contemporary Anesthesia Practice Series. FA Davis, Philadelphia, 1987, 257 pp, \$35.00.

Gravenstein JS, Newbower RS, Ream AK, Smith NT. The Automated Anesthesia Record and Alarm Systems. Stoneham MA: Butterworths, 1987, 287 pp, \$38.95.

Kaplan JA, ed. Cardiac Anesthesia, 2nd edition, 2 volumes. Orlando: Grune & Stratton, 1987, 1122 pp, \$125.00.

Morgan B, ed. Problems in Obstetric Anesthesia, Vol 3 in Perinatal Practice Series. New York: J Wiley & Sons, 1987, 198 pp, \$50.00.

Ostheimer GW, ed. Obstetric Analgesia and Anaesthesia, I & II, Vol 4, No 1 & 2 of Clinics in Anaesthesiology. Philadelphia: WB Saunders, 1986, 440 pp, \$25.95 each.

Reves JG, ed. Acute revascularization of the Infarcted Heart. Orlando: Grune & Stratton, 1987, 88 pp, \$25.00.

Short CE, ed. Principles & Practice of Veterinary Anesthesia. Baltimore: Williams & Wilkins, 1987, 669 pp, \$62.50.

Stewart JD. Focal Peripheral Neuropathies. New York: Elsevier, 1987, 420 pp, \$55.00.

Stoelting RK. Pharmacology and Physiology in Anesthetic Practice. Philadelphia: Lippincott, 1987, 859 pp, \$65.00.

Vital C, Vallat JM. Ultrastructural Study of the Human Diseased Peripheral Nerve, 2nd Ed. New York: Elsevier, 1987, 290 pp, \$58.00.

A Guide for Authors

Manuscripts should be sent to:

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2. *Personal author(s) books and monographs*
Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
3. *Chapter in a book*
Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: WB Saunders, 1974:457-72.

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 1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
 2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

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ANAESTHESIA IN THE ELDERLY

Harold T. Davenport, M.B., Ch.B.

Consultant Anaesthetist

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More and more geriatric patients are coming into the operating room. **Anaesthesia in the Elderly** addresses the many problems that an anesthesiologist needs to understand for the safe and practical management of these patients.

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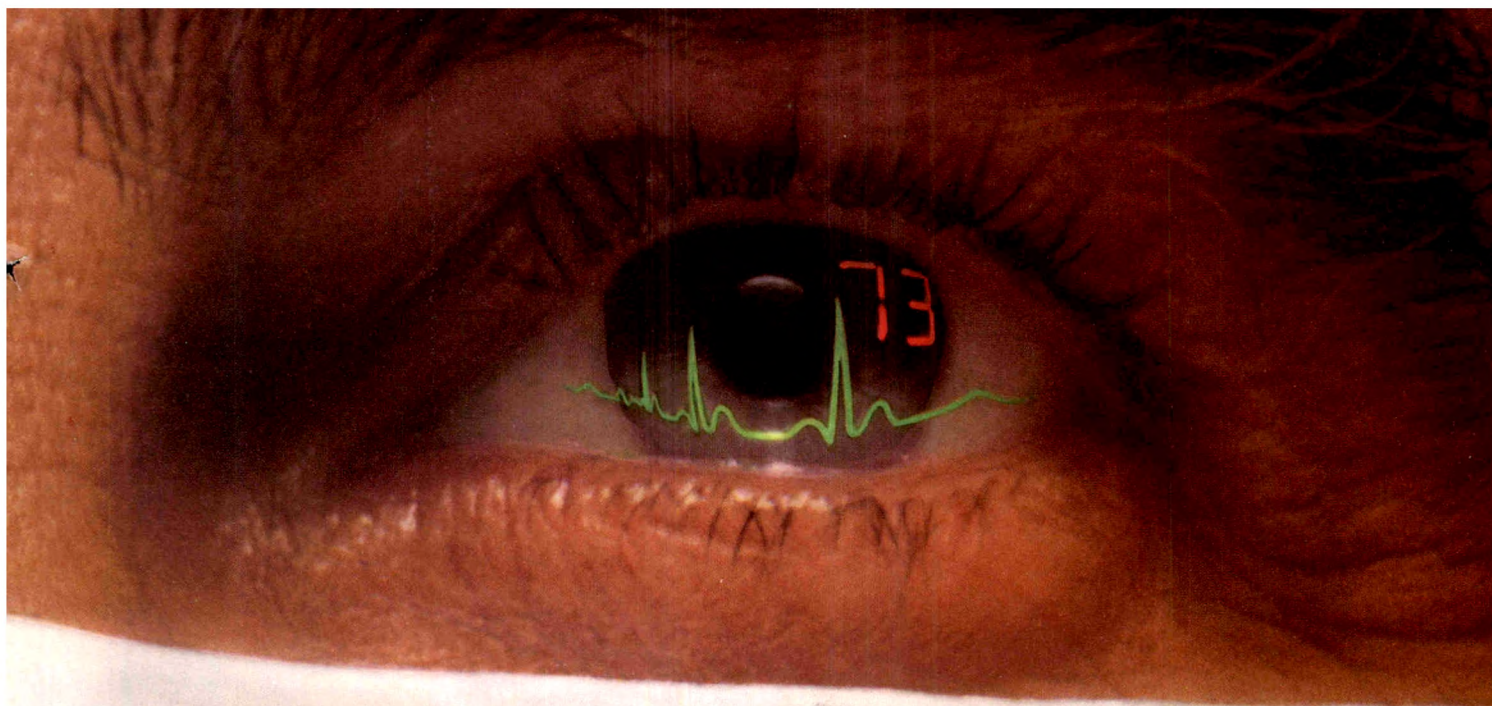
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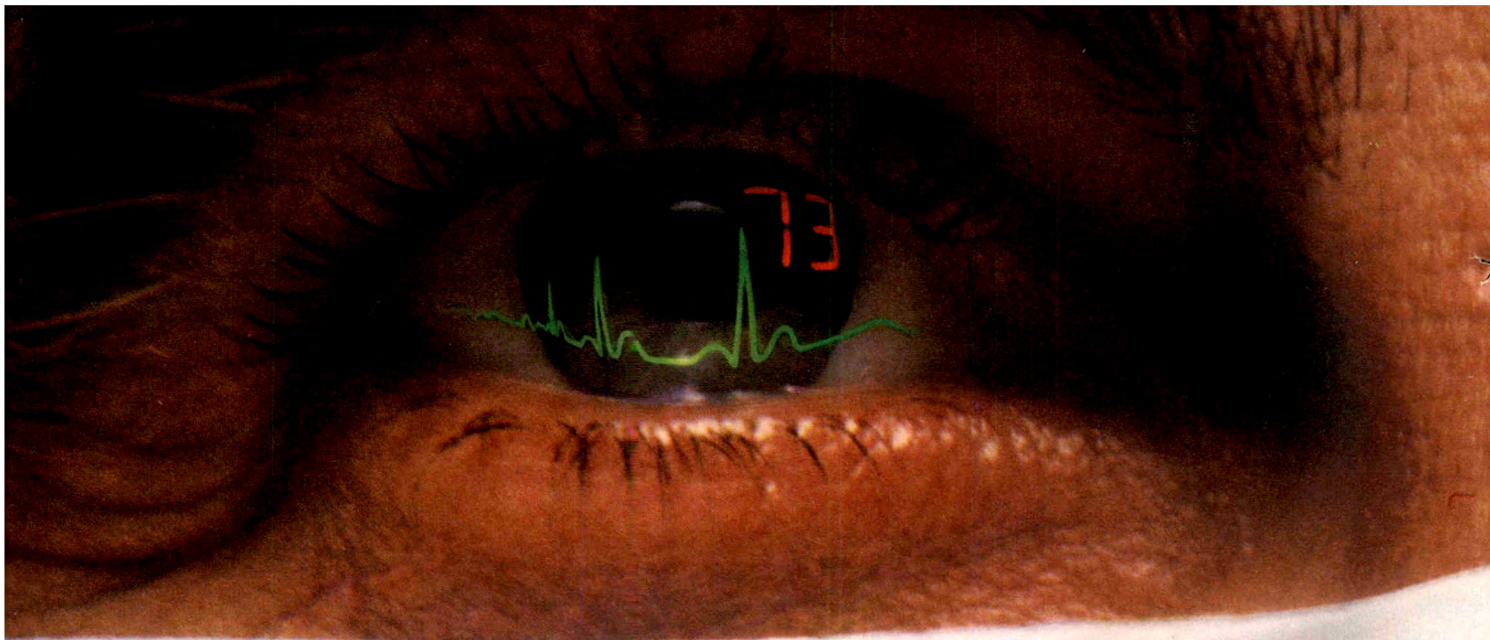
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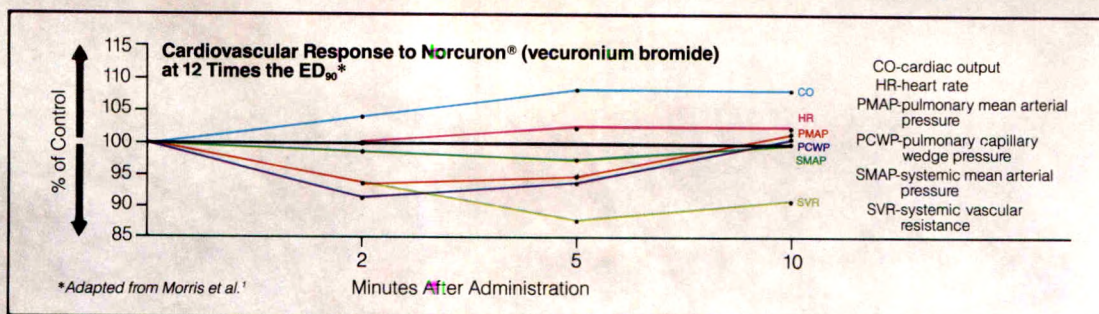
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See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.¹⁻⁴ In fact, even at 12 times effective doses, under halothane anesthesia,¹ NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.

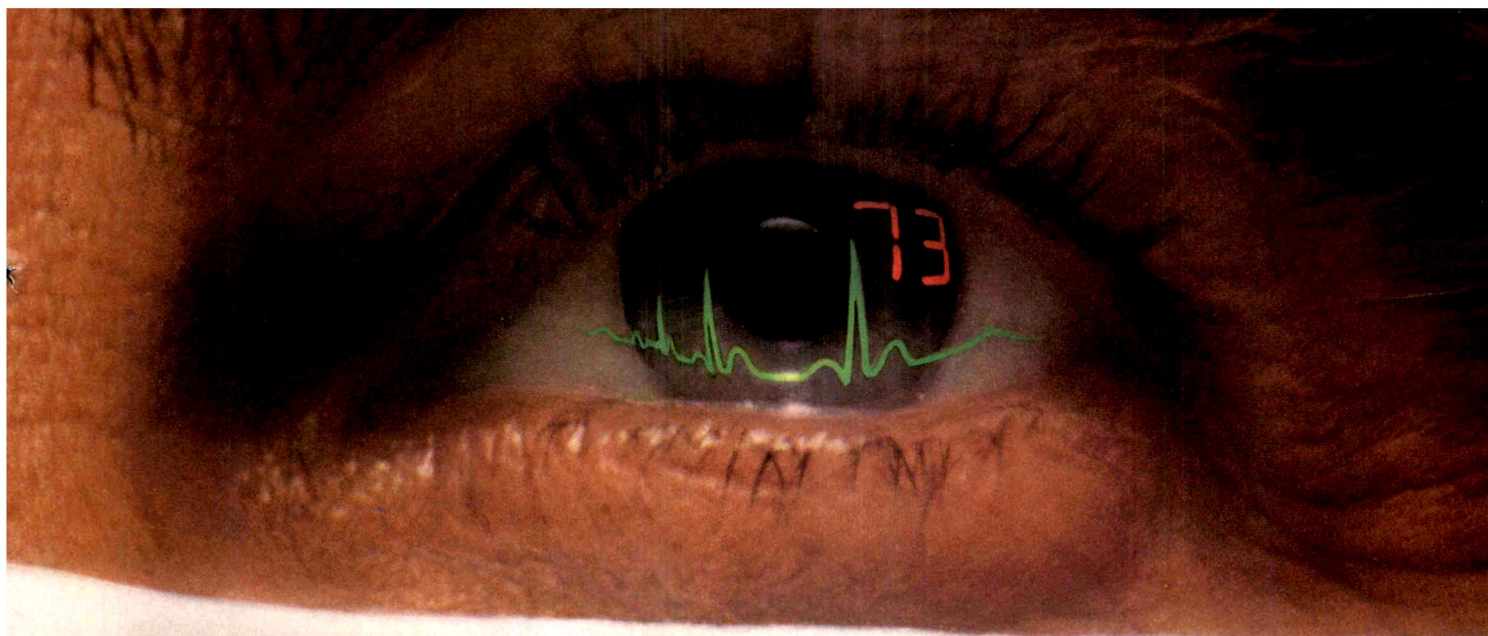


Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED₉₅.⁵

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.⁵

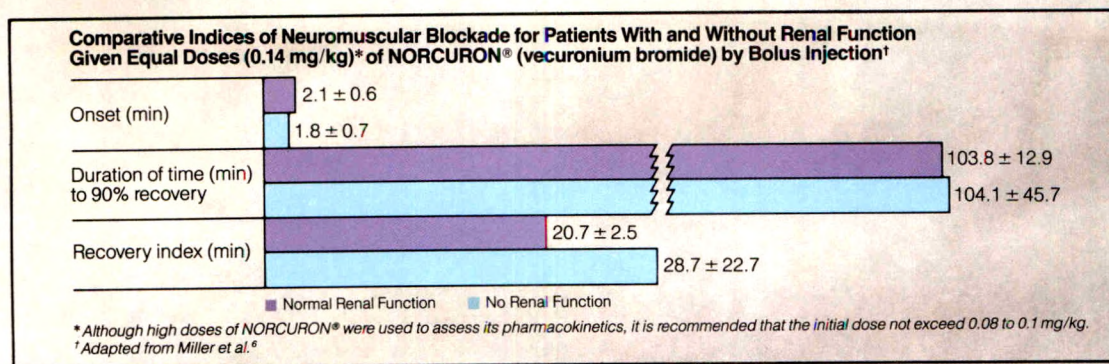
The Effect of Nondepolarizing Muscle Relaxants*				Percent of Control		
Drug	Dose (mg/kg)	xED ₉₅	Histamine	Mean Arterial Pressure	Heart Rate	
Tubocurarine	0.5	1	410	78	116	
Metocurine	0.5†	2	212	79	119	
Atracurium	0.6†	3	192	80	108	
Vecuronium	0.1	1.7	117	100	99	
Vecuronium	0.2	3.5	87	99	102	

*Adapted from Basta et al.⁵
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.⁶

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.⁶



**The surgical muscle relaxant
ideal for virtually all patients
including those at risk.**

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. 2. Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. 3. Krieg N, Crul JF, Booi LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of

vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. 5. Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. 6. Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide)*. Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2B 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstano-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED₅₀ (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect or the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose. 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolic of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution

5% glucose in water

5% glucose in saline

Lactated Ringer's

injection as the diluent. Boxes of 10 (NDC #0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC #0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

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Complete

Without any other agent or premedicant, isoflurane provides every action required for a complete anesthetic, on a closely controlled, breath-by-breath basis: unconsciousness, surgical analgesia, amnesia, and good surgical muscle relaxation—a useful advantage for laparoscopies and orthopedic work, and one that begins when the anesthetic begins and ends with elimination of the anesthetic, thereby decreasing the risk of residual paralysis in the PAR.

Because isoflurane is a complete anesthetic when given alone in oxygen or room air, nitrous oxide can be eliminated if you choose. Isoflurane anesthetics are seldom complicated and prolonged by postoperative nausea and vomiting.

FORANE[®] (isoflurane, USP)



Excellent Safety Profile

Stability of heart rhythm and good cardiac output are notable features of an isoflurane anesthetic. CNS excitation does not occur at any concentration or PaCO_2 level. Virtually 100 % of isoflurane is exhaled unchanged from the patient (only 0.17 % of the isoflurane taken up is recovered as metabolites). This near absence of metabolic by-products all but assures an absence of hepatic or renal toxicity from metabolism.

Anaquest



For outpatient anesthesia

FORANE® (isoflurane, USP)

Rapid...Complete...Excellent Safety Profile

CAUTION Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing as a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is



Some physical constants are

Molecular weight	184.5
Boiling point at 760 mm Hg	48.5 °C (unaccl.)
Refractive index n_D^{20}	1.2990-1.2995
Specific gravity 25 °/25 °C	1.496
Vapor pressure in mm Hg**	20 °C 238 25 °C 295 30 °C 367 35 °C 450

**Equation for vapor pressure calculation

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where} \quad \begin{array}{l} A = 8056 \\ B = -1664.58 \\ T = ^\circ\text{C} + 273.16 \text{ (Kelvin)} \end{array}$$

Partition coefficients at 37 °C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	9.8

Partition coefficients at 25 °C - rubber and plastic

Conductive rubber/gas	62.0
Butyl rubber/gas	76.0
Polyvinyl chloride/gas	10.0
Polyethylene/gas	2.0
Polyurethane/gas	1.4
Polyolefin/gas	1.1
Butyl acetate/gas	2.5

Purity by gas chromatography

Lower limit of flammability in oxygen or nitrous oxide at 9 pps/sec and 23 °C

Lower limit of flammability in oxygen or nitrous oxide at 900 pps/sec and 23 °C

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave UV light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali. Indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N ₂ O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO₂, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 ml of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O.

See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (not canister). PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are, in general, dose-dependent extensions of pharmacophysiological effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdose, or what may appear to be overdose, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- vaporizers calibrated specifically for isoflurane,
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ Isoflurane} = \frac{100 P_A F_V}{F_T (P_A - P_V)}$$

where P_A = Pressure of atmosphere
 P_V = Vapor pressure of isoflurane
 F_V = Flow of gas through vaporizer (mL/min)
 F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 1 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0336

Revised 10-85

Anaquest Forane® (isoflurane, USP)



Anaquest
 2005 West Beltline Highway
 Madison WI 53713 2318
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 A Division of BOC Inc

BOC Health Care

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1988 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to \$25,000 are invited for the 1988 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **December 8, 1987**.
- The official application for the Award must be used. This form, and the guidelines for applicants, are available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1988 Award(s) will be announced at the Annual Scientific Meeting (62nd Congress) of the International Anesthesia Research Society to be held at the Hotel Inter-Continental, San Diego, California, March 5-9, 1988.

The MIDWEST ANESTHESIA CONFERENCE (M A C)

May 12th-14th, 1988
Hyatt Regency Hotel
Chicago, Illinois

The ILLINOIS SOCIETY OF ANESTHESIOLOGISTS announces the Twenty-Fifth Annual MIDWEST ANESTHESIA CONFERENCE. The conference is to be held on Thursday, May 12th 1988 thru Saturday, May 14th 1988 at the Hyatt Regency Hotel in Chicago, Illinois.

The three day program will present current topics in Anesthesiology in the form of mini-courses general sessions and panel discussions by renowned experts. Social activities have been planned to include a tour of the new, major Anesthesiology exhibit "THE CONQUEST OF PAIN" in the Museum of Science and Industry in Chicago.

For further information write to:

MIDWEST ANESTHESIA CONFERENCE
G P Goldstein Conference Manager
P.O. Box 810
Algonquin, Illinois 60102

LOCUM TENENS and PERMANENT ANESTHESIOLOGISTS

Aramco's Dhahran Health Center in Saudi Arabia needs Anesthesiologists to join a staff of nine Anesthesiologists and five Nurse Anesthetists. **Locum assignments** are available for 1-3 months and Board Certification is required. A **full-time position** is also available. American Board Certification and a minimum of 2 years experience after residency required.

Our modern 483-bed hospital, JCAH accredited since 1956, has all major specialty services as well as most subspecialties and functions as a referral center for a patient population of approximately 200,000. The medical services organization includes four district clinics, one with a new 80-bed hospital.

These positions offer state-of-the-art health care facilities in a multi-national environment. The locum contractor, in addition to daily compensation rate, receives a living allowance, housing, 4 paid travel days and transportation from and to contractors point of origin. Permanent positions offer a comprehensive benefits package.

For immediate consideration, call **Velma Guy at 1-800-231-7577, ext. 8060 or 713-432-8060**. Or send resume to **Velma Guy, Aramco Services Company, Dept. 07G-034-7, P.O. Box 4530, Houston, Texas 77210-4530**.

ARAMCO

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MDAS OR CRNAS: TRANS-AMERICAN ANESTHETISTS, WEST

Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, cooperative, licensed, insured professionals caring about you. Call 1-800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303-598-2788 (CO).

ROCKY MTS./SOUTHWEST

We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, PO Box 5719, Santa Fe, NM 87501. (505) 983-7371.

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:

Individual or small group sessions given in New York City, San Francisco, and Palm Springs. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Call 415-321-1117.

PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS

Send name, address, and phone to Box ANA 5-84-E, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510. Or phone 718-727-9690.

SOUTHWESTERN PA ANESTHESIOLOGIST BE/BC to join group. All except open heart. Opening immediately. Excellent compensation and future for right person. Response confidential. Pittsburgh area. Submit CV to Box L26, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

ORAL BOARD REVIEW

Practice exams with critique. Intensive weekend course in Tampa, FL. Next class Dec. 4-6, 1987. Two instructors. Limited class size. Reply: 2656 Gunckel Bl., Toledo, OH 43606, or (419) 729-6325; (419) 475-9641—evenings.

ANESTHESIOLOGIST

Board certified or eligible to join a group of five Anesthesiologist and six Nurse Anesthetists. 350-bed modern hospital in Fredericksburg, Virginia. One hour from Washington, D.C. Reply to Dr. Robert A. Kravetz,

2101 Fall Hill Avenue, Fredericksburg, VA 22401. Or phone (703) 371-2736.

ANESTHESIOLOGISTS & CRNAs

Are you ready for "New Beginnings"? John Paju, CRNA, has been successfully placing his colleagues (both MD and CRNA) into hundreds of temporary and permanent positions throughout the US since 1969. For that personal and helpful touch call John or one of our Placement Coordinators at 1-800-FAST-GAS to discuss exciting job potentials. Send your resume to 619 South State Street, Ukiah, CA 95482. Placements are paid by the employer!

ABA ORAL EXAM REVIEW IN SCOTTSDALE

This weekend course will stimulate, challenge, educate, and prepare candidates for the oral exam, using case discussions. Recent significant research articles will be discussed. Special separate sessions for FMGs with language difficulties. Limited class size. Call for dates and information (602) 264-6340

DIRECTORSHIP

Boarded anesthesiologist needed to head fee-for-service group. East Central Illinois college town. Busy 210-bed hospital with patient draw 100,000. Send CV to Bill Rauf, SBLHC, Box 372, Mattoon, IL 61938.

MID-ATLANTIC REGION ANESTHESIOLOGIST

Professional corporation with large practice in excellent medical environment is seeking anesthesiologists with broad clinical experience and high academic achievement obtained in quality medical schools and residency programs. Expanding practice, excellent financial package. No open-heart, little OB and pediatrics. Boards now or in immediate future a must. Unusual opportunity for qualified physician. All inquiries should contain CV and references. Please reply to Box GG26, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

WEST VIRGINIA

Anesthesiologist: Board certified or eligible to join four Anesthesiologists and staff of CRNAs in facility with both in-patient and out-patient surgery. Experience in open-heart surgery or cardiac anesthesia fellow

desirable. Fee-for-service and partnership opportunity. Please submit CV and references to Monongalia Anesthesia Associates, c/o Judith Pixler, 1200 J D Anderson Drive, Morgantown, WV 26505; phone (304) 598-1245.

NORTHWESTERN UNIVERSITY MEDICAL CENTER

is recruiting faculty interested in academic careers in Anesthesia. Candidates must have completed at least 4 years of postgraduate training and be Board certified or in the process of certification. Evidence of scholarly productivity will be considered in making final selections. A strong residency program with fellowships in all clinical subspecialties makes appointment to this faculty desirable. Equal opportunity employer. Send curriculum vitae and names of three references to Edward A. Brunner, MD, PhD, Professor and Chairman, Department of Anesthesia, Northwestern University Medical School, 303 East Superior Street, Room 360, Chicago, IL 60611.

FREELANCE ANESTHETISTS

Temporary and permanent—Medical Anesthesiologists—CRNAs/Home-based throughout the United States. If you need an anesthetist, call (800) 521-6750, ALL-STATES MEDICAL PLACEMENT AGENCY, Box 91, LaSalle, MI 48145, or (313)241-1418 (MI).

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum 1/4 page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: \$1.00 per word, minimum twenty words. Additional fee of \$12.00 for box number ads. Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be typed double-spaced and mailed in duplicate to:
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RESEARCH AND INTENSIVE CARE

Maimonides Medical Center (Affiliate for Downstate SUNY Medical School) recruiting anesthesiologists in research and intensive care areas. Department has active residency program with cardiac, OB, and pain. Looking to expand in research and intensive care areas. Send information to: Ketan Shevde, MD, Acting Director, Department of Anesthesia, Maimonides Medical Center, 4802 Tenth Avenue, Brooklyn, NY 11219.

TENNESSEE ANESTHESIOLOGIST

Directing Anesthesia services of large Regional Medical Center including Labor and Delivery, Trauma Center, Ambulatory, and Operating Rooms. Full-time faculty position in University with emphasis on teaching, patient care, and research. Faculty position: Assistant Professor-Associate Professor, salary commensurate. Must be diplomate of ABA. Must meet Tennessee license requirements. Interest and experience in teaching, patient care, and management preferred. Excellent opportunity for private practice with teaching and research activities. Send CV, bibliography, and three references to: John J. Angel, MD, Chairman, University of Tennessee, Memphis, Department of Anesthesiology, 800 Madison Avenue, Memphis, TN 38163. AA/EEO Employer.

TENNESSEE

Pediatric Anesthesiology—Full-time position at level of Instructor/Associate Professor with emphasis on teaching, patient care, and clinical research. Assigned to large Children's Medical Center. Must meet Tennessee license requirements and ABA diplomate or eligible for ABA exam. Send C.V., bibliography, and three references to: John J. Angel, MD, Chairman, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, FG17, Memphis, TN 38138. AA/EEO Employer.

MIDWEST WATERFRONT CITY

Fee-for-service group of MDs seeks new partner who is board eligible or certified to practice in 650-bed medical center with minimal obstetrics. Midwest location in progressive waterfront city. Please reply to Box HH31, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

ANESTHESIA RESEARCH

The Department of Anesthesiology at Loyola University Stritch School of Medicine, Maywood, Illinois, located in the western suburbs 10 miles from downtown Chicago, is recruiting one faculty member with established research experience and/or a strong desire to pursue research in Anesthesia. Excellent laboratory support is in existence.

Minimum requirements are Board Certification in Anesthesiology with experience in teaching, research, and clinical training, and Illinois state licensure or eligibility. Appointment will be at the level of Associate Professor or Professor. Salary commensurate with qualifications and experience. Please send letter, curriculum vitae, and names/addresses of three references to: T.L.K. Rao, MD, Chairman, Department of Anesthesiology, Loyola University Stritch School of Medicine, 2160 South First Avenue, Maywood, IL 60153. Loyola Medical Center is an equal opportunity employer.

ILLINOIS

Academic department seeking additional faculty at level of Assistant or Associate Professor. Candidates should be qualified in clinical care, teaching, and research. Minimum requirement is a 4-year educational continuum or its equivalent. Faculty rank and salary commensurate with training and experience. Send Curriculum Vitae to: T.L.K. Rao, MD, Chairman, Department of Anesthesiology, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153.

PENNSYLVANIA

BC/BE Cardiac Anesthesiologist to join a group of six anesthesiologists and 18 CRNAs in a community hospital of 450 beds doing approximately 800 cardiac cases per year. Minimum requirements include fellowship training in cardiac anesthesia and PA state licensure or eligibility. Send CV to: Jack A. Scott, MD, Department of Anesthesiology, 5230 Centre Avenue, Pittsburgh, PA 15232.

MARYLAND

Anesthesiologist BC/BE sought for three-member group serving modern 200-bed community hospital. Six CRNAs. 4,000 cases/year. All surgical subspecialties except cardiac. Regional trauma center. Moderate OB. Active new outpatient surgery unit within hospital. Community of 25,000 in mountains of Western Maryland. Close to four-season recreational opportunities. Position available January 1988, but will wait for right person. Salary first, leading to partnership. Send CV and references to: W.R. Hodges III, MD, Department of Anesthesia, Memorial Hospital and Medical Center, Cumberland, MD 21502.

BOARD-CERTIFIED ANESTHESIOLOGIST

Northeastern Ohio teaching hospital with an approved, 4-year residency program in anesthesiology seeks a board-certified anesthesiologist with extensive interest and experience in research and teaching. Responsibilities will include clinical practice, house staff education, and clinical investigation.

Excellent salary and benefits leading to early partnership. Send curriculum vitae and references to: John G. Poulos, M.D., Chairman, Department of Anesthesiology, Huron Hospital, 13951 Terrace Road, Cleveland, OH 44112.

PRIVATE PRACTICE IN OHIO

Anesthesiologist for private practice in an established group serving a modern, well equipped community hospital in Ohio. Small city near metropolitan areas. Send CV and current references to: Box HH32, c/o *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

RESPIRATORY THERAPY SECTION CHIEF

Board Eligible or board certified anesthesiologist wanted to be Section Chief of Respiratory Therapy Department. Duties limited to above. Formal training required. Please reply to Box HH33, c/o *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

VAIL, COLORADO

Immediate opening for anesthesiologist in beautiful Vail, Colorado. Vail Valley Medical Center is a community hospital serving the greater Vail area. No neuro or cardiac. This is an excellent fee-for-service position in a mountain community with superb recreational opportunities. Send all inquiries, with resume, to: Ray McMahan, 181 West Meadow Drive, Vail, CO 81657.

CHAIRMAN, ANESTHESIA DEPARTMENT

Bridgeport CT: 600-bed university affiliated teaching hospital is seeking a chairman, Department of Anesthesiology Residency Program and Masters Program for CRNA. 14 attending anesthesiologists on staff with full complement CRNAs. Academic and administrative experience required with demonstrated evidence of clinical excellence. 14,000 anesthetics administered yearly with all surgical specialties. Send CV to Bruce McDonald, MD, Chairman, Anesthesia Search Committee, Bridgeport Hospital, 267 Grant St., PO Box 5000, Bridgeport, CT 06610.

ANESTHESIOLOGIST

Board certified/eligible individual needed for 300-bed teaching hospital with a full range of surgery except open-heart. Please send curriculum vitae to: S.K. Reddy, MD, St. Louis Regional Medical Center, 5535 Delmar Blvd., St. Louis, MO 63112.

IOWA: NEUROANESTHESIA FELLOWSHIPS

The Neuroanesthesia Group at the University of Iowa Hospitals and Clinics is taking applications for 1988-89. The group provides >1500 neurosurgical anesthetics/yr, and three funded laboratories. OR projects concerning hemodynamics, electrophysiology, and pharmacology are underway, while laboratory efforts are ongoing in the cerebrovascular and metabolic physiology anesthetics and ischemia/trauma, and in neuromuscular pharmacology. Methods available include neurohistology, autoradiography (CBF and CMRG), H₂ clearance (CBF), processed EEG and EP, microgravimetry, voltage clamping. Fellows are expected to participate in clinical and/or laboratory research, and should have completed at least 24 months of approved Anesthesia residency training. Contact Michael M. Todd, MD, or David S. Warner, MD, Neuroanesthesia Research Group, Department of Anesthesia, University of Iowa Hospitals and Clinics, GH65E, Iowa City, IA 52242.

ANESTHESIOLOGIST

Large Chicago area hospital with a residency program seeks a qualified attending anesthesiologist with strong interest in teaching and research. Very competitive salary and fringe benefits, commensurate with experience. Board certification and 4 years' training preferred. Please send curriculum vitae to Box HH34 c/o *Anesthesia and Analgesia*, 333 Cedar Street, New Haven CT 06510.

AAA ANESTHESIOLOGIST

To confidentially explore salaried and contract positions available at our facilities in the U.S., reply with CV and include availability date, licensure status, and geographical preference. NAMA Professional Bldg., Suite 200, 138 East Street, Carlisle, MA 01741.

SOUTHERN CALIFORNIA

The Beaver Medical Clinic, Inc., A 34-physician multispecialty group practice located in Southern California is currently recruiting a well-trained anesthesiologist to join its Anesthesiology Department. Group's anesthesia work in call schedule of 7-man anesthesia staff in support of the 200-bed Community Hospital and free-standing Surgery Center. Liberal guaranteed starting salary with productivity bonus compensation package, malpractice paid. Excellent fringe benefit package and potential shareholder status within 2 years. Practice located in family oriented community with ideal opportunity for year round outdoor activities. Send CVs to: Beaver Medical Clinic, Inc., ATTN: Melanie Vale, 2 West Fern Avenue, Redlands, CA 92373.

KENTUCKY

The Department of Anesthesiology, University of Kentucky in Lexington is seeking additional faculty. We are recruiting qualified physicians for critical care medicine and cardiothoracic anesthesia programs. Applicants must be board eligible/certified, interested in medical student and resident teaching as well as clinical research. Excellent salary and fringe benefit program. Please reply with curriculum vitae to: William O. Witt, MD, Chairman, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, KY 40536-0084.

DEPARTMENT CHAIRMAN

Louisiana The Anesthesiology Department of the Louisiana State University Medical Center has an opening for a department chairman with interest in an academic setting. The position's duties include instruction and supervision of residents and students and administration of a large academic department. Qualifications must include graduation from a LCME accredited medical school, completion of an approved residency training program, eligibility for Louisiana medical licensure, and board certification. Administrative experience or excellent recommendations regarding administrative capabilities are required. The candidate must possess an excellent clinical record and manifest an interest in academics and research. Specialty training or experience is desired. The salary and level of faculty appointment will be commensurate with qualifications. Inquiries should be directed immediately along with a current Curriculum Vitae to: Fred J. Stucker Jr., MD, Chairman of the Search Committee, Louisiana State University Medical Center in Shreveport, PO Box 33932, Shreveport, LA 71130-3932. Affirmative Action/Equal Opportunity Employer.

BOULDER, COLORADO

38-Physician multispecialty group practice is seeking an anesthesiologist with administrative skills to be the Anesthesiologist/Director of its Ambulatory Surgical Unit. Send qualifications to Dr. John Avery, Boulder Medical Center, 2750 Broadway, Boulder, CO 80302.

ANESTHESIOLOGIST

BC/BE to join group of 11 MDs with CRNAs in a large hospital located in a pleasant mid-western community on the Great Lakes. Busy practice covering all major surgical subspecialties plus respiratory/ICU involvement and minimal OB. Excellent starting salary and benefits package leading to early partnership. Reply to Box HH35, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

UNIVERSITY OF CALIFORNIA, SAN DIEGO

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Anesthesiology: The University of Nebraska Medical Center has three faculty positions available for board certified/board eligible anesthesiologists. Academic rank and salary commensurate with education and experience. Fellowship training and/or experience in research and teaching required. Specific need exists for anesthesiologists with liver or heart transplant experience who can assist and develop research projects in these areas. Candidates must be eligible for Nebraska medical licensure. Interested applicants should send curriculum vitae and two letters of reference to: Dennis F. Landers, MD, PhD, Interim Chairman, Department of Anesthesiology, University of Nebraska Medical Center, 42nd & Dewey Avenue, Omaha, Nebraska 68105. Affirmative Action/Equal Opportunity Employer.

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BC/BE anesthesiologist needed for full-time position at the University of Louisville, Louisville, Kentucky. Concentration will be on critical care and research. Must meet Kentucky licensure requirements. Competitive salary and fringe benefits. Applicants send curriculum vitae to: Benjamin M. Rigor, MD, Professor and Chairman, Department of Anesthesiology, University of Louisville, Louisville, Kentucky 40292. The University of Louisville is an Affirmative Action Equal Opportunity Employer.

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The University of Arizona Department of Anesthesiology is establishing a new residency training program in Phoenix. Qualified anesthesia faculty are sought both for tenure and clinical tracks at all levels for operating room, ICU, and OB activities in Phoenix. Female and minority applicants are welcome. Contact: Burnell R. Brown Jr., MD, PhD, Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ, 85724. Equal Employment Opportunity/Affirmative Action Employer. Closing date: 12/31/87.

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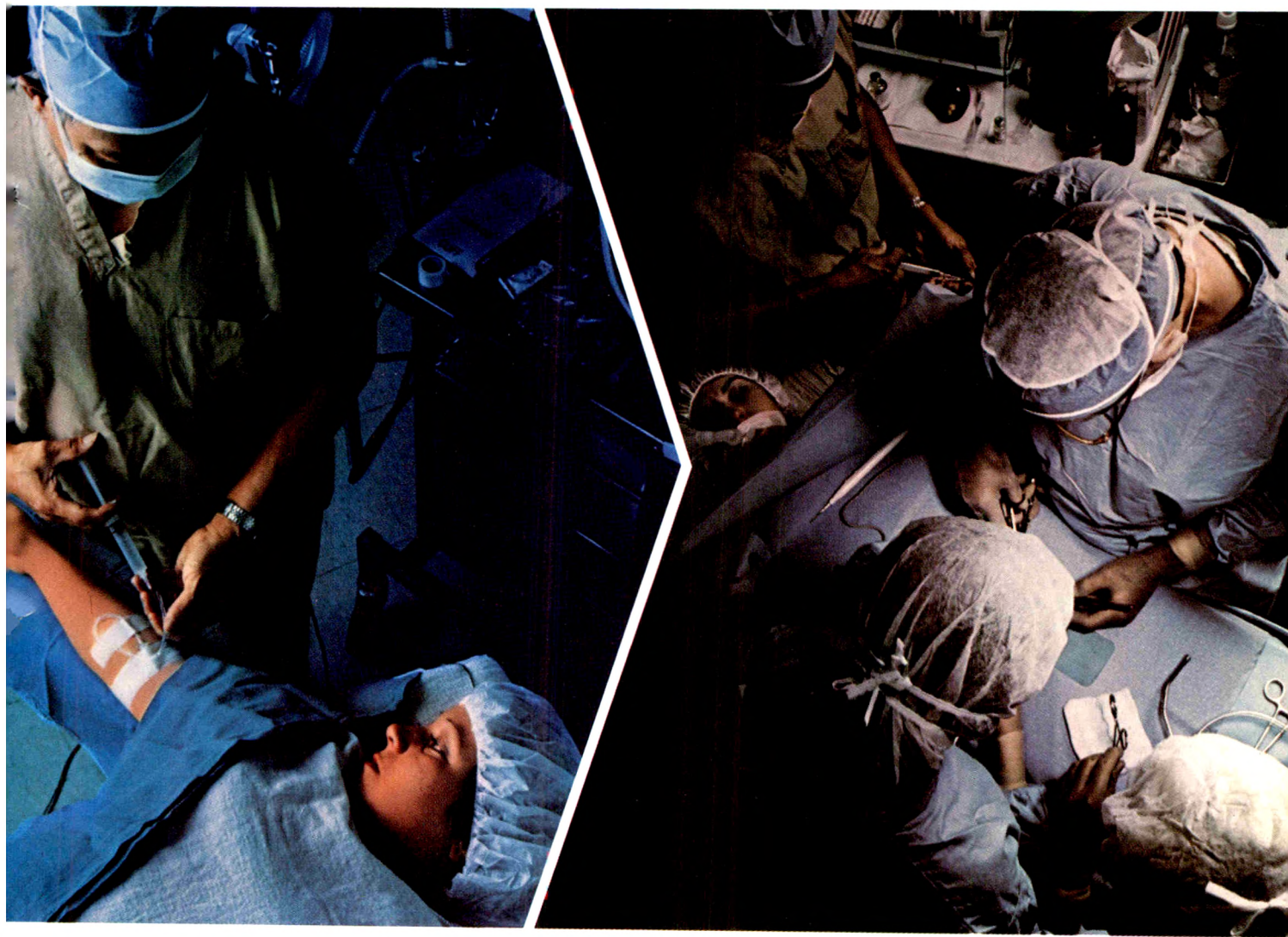


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INJECTION**

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: **IM:** preoperative sedation, to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents, as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen and resuscitative equipment for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Do not administer in shock, coma, acute alcohol intoxication with depressed vital signs. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic. Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by about 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia. VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication. A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

VERSED® (brand of midazolam HCl/Roche)

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted. A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects. Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred (See WARNINGS). In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported (See DOSAGE AND ADMINISTRATION).

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccups (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: **Respiratory:** Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. **Cardiovascular:** Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. **Gastrointestinal:** Acid taste, excessive salivation, retching. **CNS/Neuromuscular:** Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. **Special Sense:** Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. **Integumentary:** Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. **Miscellaneous:** Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients (See WARNINGS). **IM use:** Inject deep in large muscle mass. **IV use:** Administer initial dose over 20 to 30 seconds for induction of general anesthesia. For conscious sedation administer initial dose over 2 to 3 minutes. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.



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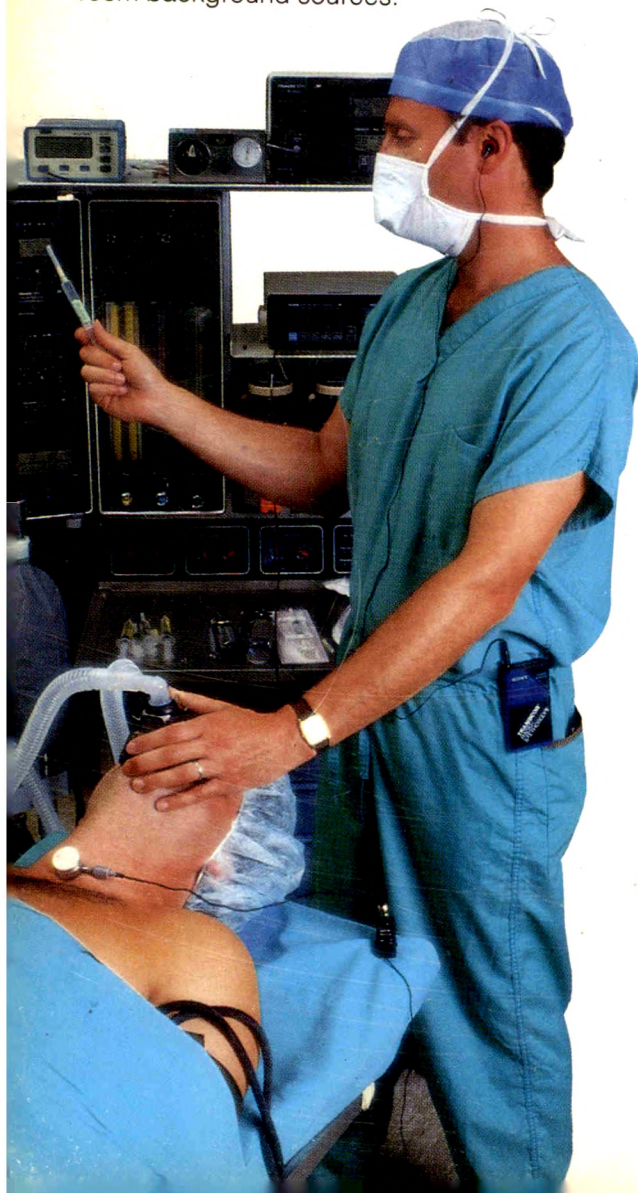
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INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and anti-shock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg/kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

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REFERENCES:

1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. I. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975.
2. Ravin MB: Pyridostigmine as an antagonist of d-tubocurarine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.



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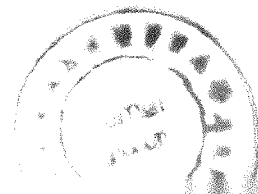
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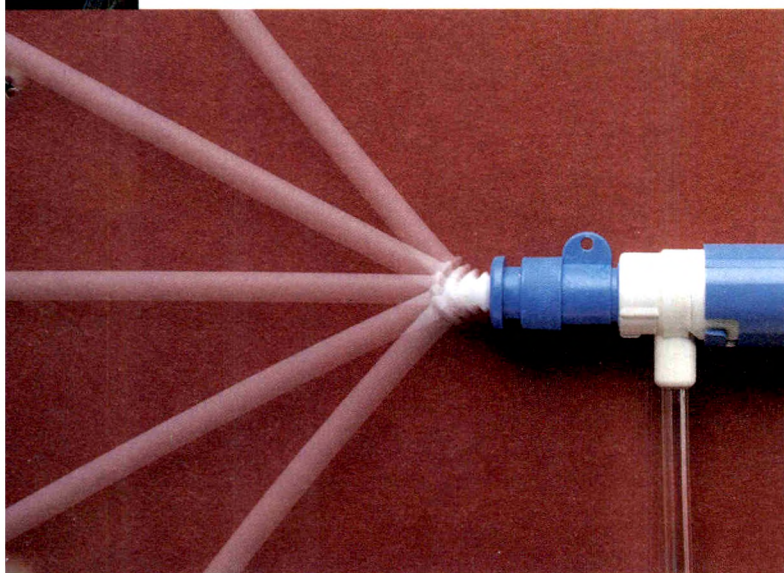
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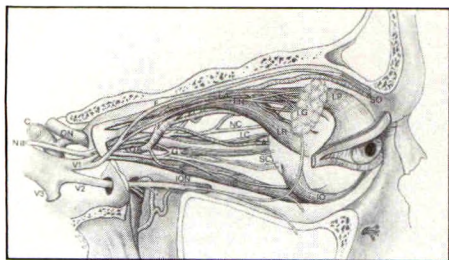
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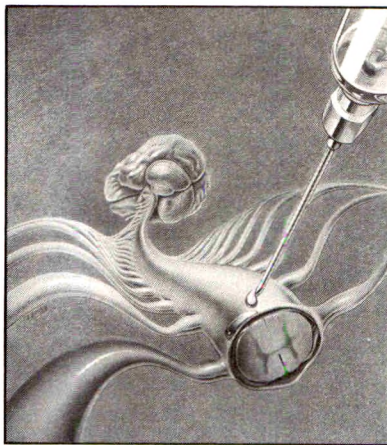
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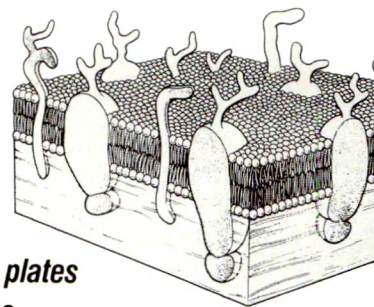
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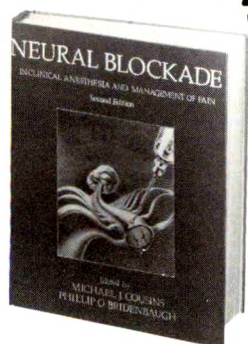
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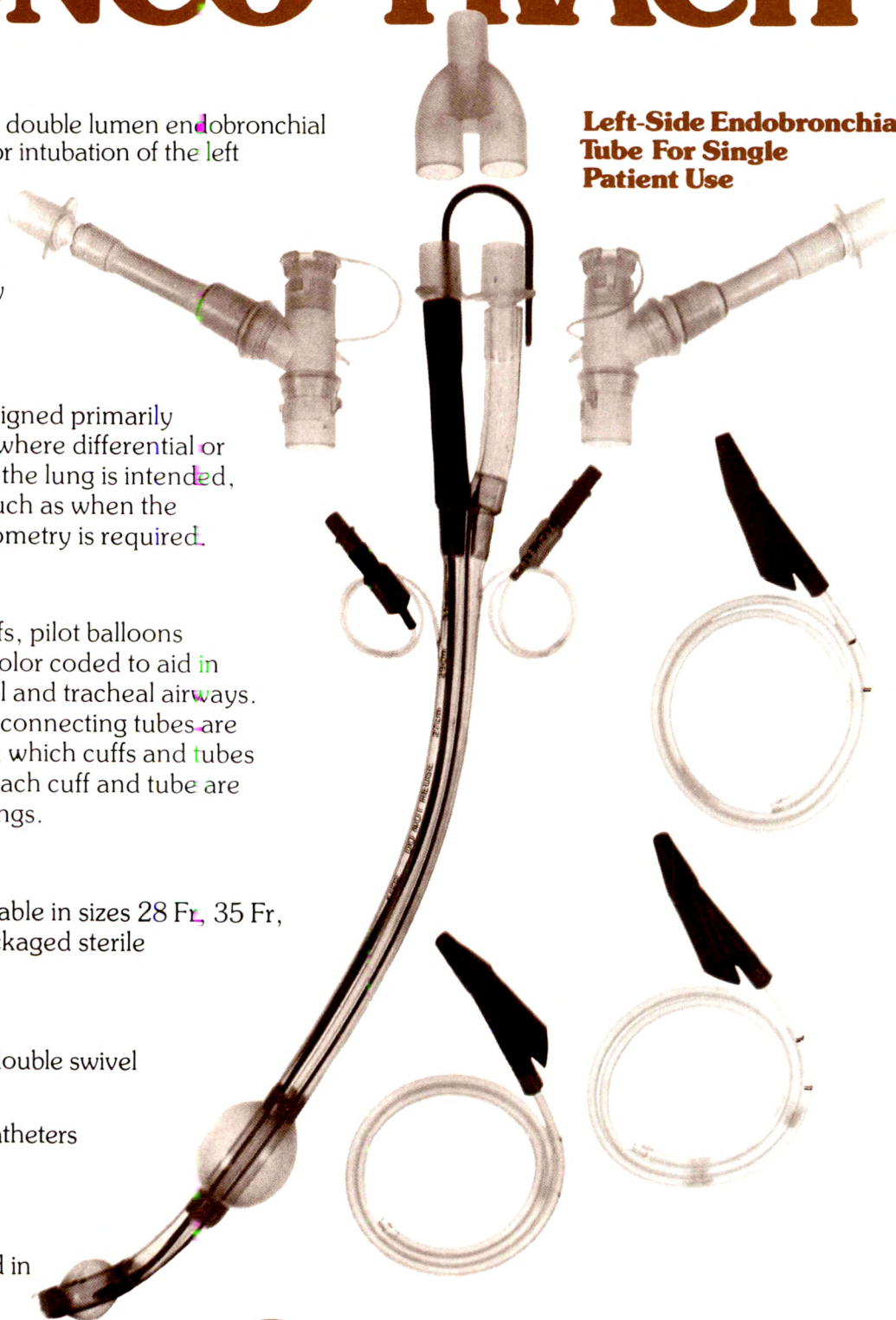
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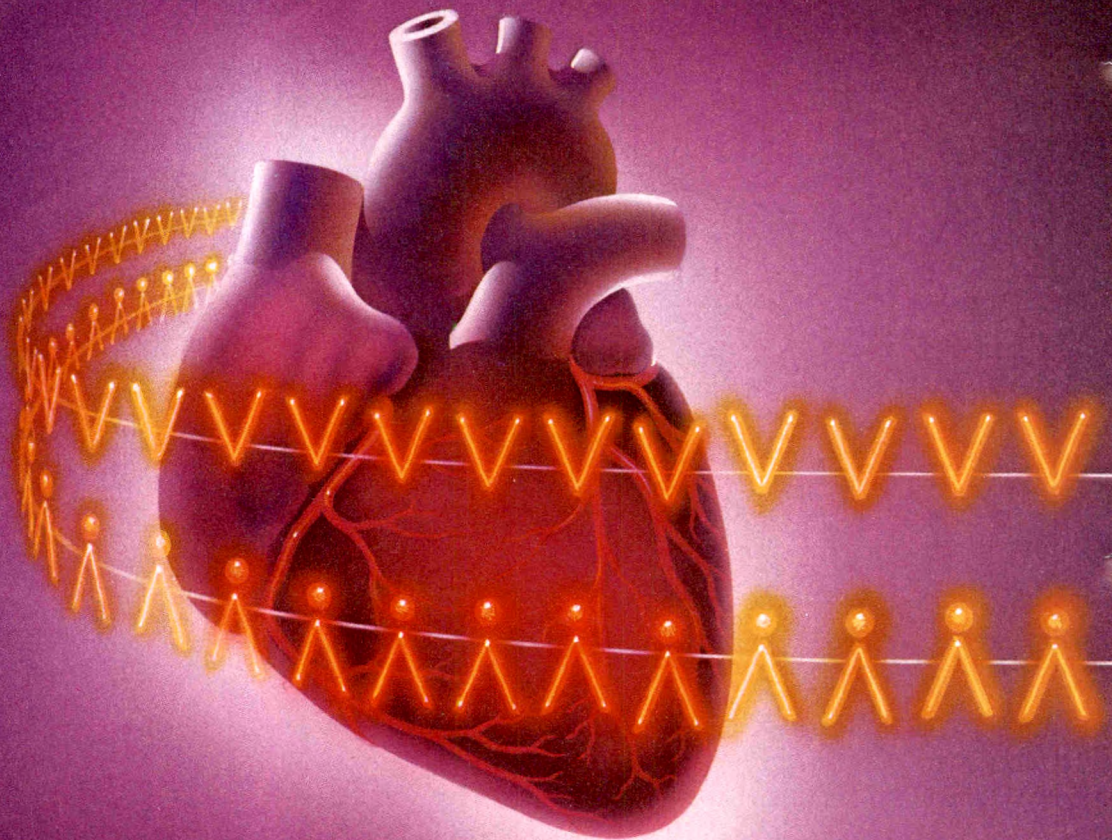
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“Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug.”⁴

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium, and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. *Anesthesiology* 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. *Anesthesiology* 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. *Br J Anaesth* 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. *Br J Anaesth* 54:375-385, 1982.

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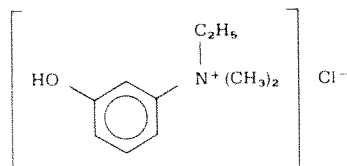
Anaquest

Enlon[®] (edrophonium chloride injection, USP)



DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdose. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdose (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdose is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarinic-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdose (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdose such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdose occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSEAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdose, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle, intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds, above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test, however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

NDC 10019-873-15 15 mL multidose vials.

A-0323

Revised 10-85

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Sufentanil Pharmacokinetics in Pediatric Cardiovascular Patients

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GREELEY WJ, de BRUIJN NP, DAVIS DP. Sufentanil pharmacokinetics in pediatric cardiovascular patients. *Anesth Analg* 1987;66:1067-72.

The pharmacokinetics of sufentanil were studied in 28 pediatric patients undergoing cardiovascular procedures. Patients were divided into four groups on the basis of age: neonates (0-1 month, $n = 9$), infants (1-24 months, $n = 7$), children (2-12 yr, $n = 7$), and adolescents (12-18 yr, $n = 5$). Sufentanil 10-15 $\mu\text{g/kg}$, was administered by IV bolus and plasma concentrations measured for up to 20 hr. A tri-exponential equation best described the time-concentration data in all patients. Clearance rate (Cl) was $6.7 \pm 6.1 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ($\pm$ SD) in neonates, which was significantly lower than the values of 18.1 ± 2.7 , 16.9 ± 3.2 , and $13.1 \pm 3.6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ observed in infants, children, and adolescents, respectively. The volume of distribution at steady state (V_{dss}) was $4.15 \pm 1.0 \text{ L/kg}$ in neonates, significantly greater than the values of 2.73 ± 0.5 and 2.75

$\pm 0.5 \text{ L/kg}$ observed in children and adolescents, respectively. The elimination half-life ($T_{1/2\beta}$) was $783 \pm 346 \text{ min}$ in neonates, significantly longer than the values of 214 ± 41 , 140 ± 30 , and $209 \pm 23 \text{ min}$ observed in infants, children, and adolescents, respectively. The plasma concentration of sufentanil at the time of additional anesthetic supplementation to suppress hemodynamic responses to surgical stimulation was 2.51 ng/ml in neonates, significantly higher than the levels of 1.58, 1.53, and 1.56 ng/ml observed in infants, children, and adolescents, respectively. The authors conclude that age-related differences in pharmacokinetic and pharmacodynamic properties of sufentanil are evident in pediatric patients with major cardiovascular disease who are undergoing cardiovascular surgery.

Key Words: ANESTHESIA—pediatric, cardiovascular. ANESTHETICS, INTRAVENOUS—sufentanil. PHARMACOKINETICS—sufentanil, pediatric.

Sufentanil is frequently used as an anesthetic agent in pediatric patients. Several studies have described its anesthetic and hemodynamic effects during pediatric cardiovascular surgery (1,2). Despite the frequent use of this opioid for anesthesia in infants and children, there are only inconclusive data describing its kinetics in the pediatric population. Previous drug studies and our clinical experience suggest age-related differences in the dose-response of opioids in children during cardiovascular surgery (3,4). Therefore, we have studied the pharmacokinetics of sufentanil in neonates, infants, children, and adolescents undergoing cardiovascular surgery.

Methods

After Institutional Review Board approval and informed parental consent, 28 pediatric patients sched-

uled for elective cardiac surgery were studied. Patient profiles and operative procedures are presented in Table 1. Exclusion criteria for our study were: 1) historical or biochemical evidence of hepatic or renal disease, 2) long-term use of enzyme-inducing drugs, e.g. phenobarbital, 3) intraoperative blood loss $>20 \text{ ml/kg}$. Patients were grouped on the basis of age: group I comprised neonates 1-30 days old; group II comprised infants, 1 month-2 yr; group III were children, 2-12 yr; group IV were adolescents, 12-18 yr.

Patients older than 9 months received meperidine 2.0 mg/kg, diazepam 0.1 mg/kg, and pentobarbital 2.0 mg/kg orally as premedication 75 min before the induction of anesthesia. Patients younger than 9 months received no premedication. Anesthesia was induced with halothane, nitrous oxide, and oxygen by mask. After intravenous and intra-arterial cannulae were placed, sufentanil 10-15 mcg/kg was administered as a rapid bolus intravenously, and the halothane and nitrous oxide were discontinued. Pancuronium 0.1 mg/kg was administered to facilitate intubation of the trachea and controlled ventilation. Ventilation was adjusted to maintain a PaCO_2 of 35-40 mm Hg, and normothermia was maintained. During surgery, an-

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Table 1. Demographic Data

Patient Number	Age	Weight (kg)	Diagnosis	Operation	Sampling Duration (min)
Group I (<i>n</i> = 9)					
1	1 days	3.0	Coarctation	Resection	1200
2	2 days	3.3	Single ventricle	BT shunt	1200
3	3 days	3.6	Transposition, PS	BT shunt	1200
4	4 days	3.1	Single ventricle	BT shunt	1200
5	7 days	3.9	Coarctation	Resection	1200
6	8 days	3.0	Coarctation	Resection	1200
7	21 days	3.5	Vascular ring	Aortic arch division	1200
8	23 days	2.8	Coarctation	Resection	1200
9	30 days	3.0	Pulmonary atresia	BT shunt	1200
Group II (<i>n</i> = 7)					
10	2 mo	3.7	Coarctation	Resection	1200
11	5 mo	5.7	Tetralogy	BT shunt	1200
12	10 mo	10	Tetralogy	BT shunt	1200
13	11 mo	7.7	Total anom. return	Repair ^a	240
14	23 mo	9.8	Double outlet RV	Glenn shunt	1200
15	23 mo	12	Coarctation	Resection	1200
16	23 mo	12	Recoarctation	Resection	1200
Group III (<i>n</i> = 7)					
17	3 yr	17	Pulmonary atresia	Glenn shunt	1200
18	3 yr	14	PS, VSD	Correction ^a	240
19	4 yr	15	Double outlet RV	Glenn shunt	1200
20	7 yr	17	Aortic stenosis	Konno procedure ^a	300
21	8 yr	27	Pulmonary atresia	Fontan ^a	300
22	9 yr	27	Pulmonary atresia	Glenn shunt	1200
23	11 yr	30	Pulmonary atresia	Glenn shunt	1200
Group IV (<i>n</i> = 5)					
24	13 yr	48	Transposition, PS	Rastelli ^a	300
25	14 yr	50	Tricuspid atresia	Glenn shunt	1200
26	16 yr	59	Tetralogy	Rastelli ^a	300
27	16 yr	65	Tricuspid atresia	PA angioplasty	1200
28	18 yr	70	Aortic stenosis	Valve replacement ^a	300

Abbreviations: BT, Blalock-Taussig; PS, pulmonic stenosis; RV, right ventricle; VSD, ventricular septal defect; PA, pulmonary artery.

^aProcedures requiring cardiopulmonary bypass.

esthetic supplementation with nitrous oxide or other narcotics was given to any patient who had an increase in heart rate or mean blood pressure >20% over baseline levels.

Arterial blood was obtained before and 1, 2, 5, 9, 11, 15, 20, 25, 30, 35, 45, 55, 80, 100, 120, 180, 240, 300, 360, 480, 600, 900, and 1200 min after sufentanil injection. For the few patients undergoing cardiac procedures requiring cardiopulmonary bypass, samples were obtained until the initiation of bypass when the time from incision to bypass equaled or exceeded 240 min. No samples were obtained during or after extracorporeal circulation. Plasma was immediately separated from blood samples and stored at -70°C until assayed. Plasma concentrations of sufentanil were determined in duplicate by radioimmunoassay (5). The sensitivity of the assay was 0.1 ng/ml. The intra-assay and interassay coefficients of variation were 2.8

and 3.4%, respectively, over a range of 1.0-3.9 ng/ml. The plasma sufentanil concentration-time curve for each patient was then fitted to bi- and triexponential equations using extended, least squares nonlinear regression analysis (6). This method allows automatic weighting of data through its ability to estimate the parameters of a parametric variance model. Log likelihood values were used to determine the best pharmacologic model. Using standard formulas as described by Gibaldi and Perrier (7), we determined the slow distribution half-life ($T_{1/2\alpha}$), the elimination half-life ($T_{1/2\beta}$), and total plasma clearance (Cl). The volume of distribution at steady state (V_{dss}) was calculated using the formula described by Wagner (8). At all sampling intervals heart rate, blood pressure, and patient response were recorded. Mean values of the pharmacokinetic data for the four groups were compared by one-way analysis of variance and Newman-

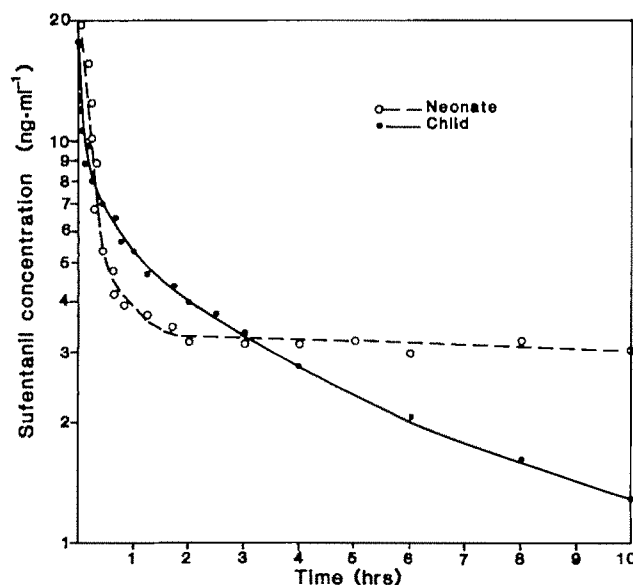


Figure 1. Representative time-plasma concentration curves from a neonate in group I and a child in group III after sufentanil bolus (10 mcg/kg).

Keuls test. Statistical significance was assumed at $P < 0.05$. Results are presented as mean values $\pm$ SD.

Results

The best fit to the time-concentration data for sufentanil was by a triexponential equation in all patients. This is demonstrated by the plasma-time concentration curves displayed in Figure 1. Pharmacokinetic data for each patient are presented in Table 2. Pharmacokinetic data for the four age groups are given in Tables 3 and 4. The $T_{1/2\alpha}$ was similar in all groups. Elimination half-life was significantly greater in group I (neonates) than in groups II (infants), III (children), and IV (adolescents). The $V_{d_{ss}}$ was greater in group I than in groups II, III, and IV. Total plasma clearance was significantly higher in groups II and III compared with the adolescent group IV. Clearance was significantly reduced in the neonatal group I. As shown by the large standard deviation values, the neonatal group had the greatest variation in the pharmacokinetic parameters studied ($T_{1/2\alpha}$, $T_{1/2\beta}$, $V_{d_{ss}}$, Cl).

Table 5 shows the pharmacodynamic data for the various age groups. Included is the plasma concentration of sufentanil at the time of additional anesthetic required for hemodynamic responsiveness due to intraoperative or postoperative stimuli. Anesthetic supplementation occurred at a significantly higher plasma sufentanil concentration in the neonatal group I compared with the other groups.

Table 2. Individual Sufentanil Pharmacokinetic Parameters

Patient No.	$V_{d_{ss}}$ (L/kg)	$T_{1/2\beta}$ (min)	Clearance (ml·kg ⁻¹ ·min ⁻¹)
Group I (n = 9)			
1	3.58	444	21.4
2	3.24	1162	8.8
3	6.26	434	4.3
4	3.64	332	6.7
5	4.71	1140	1.7
6	4.21	770	6.7
7	2.86	1099	1.2
8	4.68	869	2.5
9	4.15	382	7.3
Mean $\pm$ SD	4.15 $\pm$ 1.01	737 $\pm$ 346	6.7 $\pm$ 6.1
Group II (n = 7)			
10	4.78	145	19.0
11	2.62	250	19.6
12	2.86	257	13.3
13	2.68	252	17.4
14	2.92	201	22.2
15	1.88	204	18.7
16	3.90	190	16.8
Mean $\pm$ SD	3.09 $\pm$ 0.95	214 $\pm$ 41	18.1 $\pm$ 2.8
Group III (n = 7)			
17	2.56	191	11.7
18	2.14	138	15.6
19	2.67	130	18.8
20	2.93	159	15.4
21	3.08	133	18.7
22	3.56	138	21.9
23	2.20	92	16.5
Mean $\pm$ SD	2.73 $\pm$ 0.50	140 $\pm$ 30	16.9 $\pm$ 3.2
Group IV (n = 5)			
24	2.21	203	10.0
25	3.00	214	11.7
26	2.74	241	16.5
27	3.50	176	17.4
28	2.30	213	9.9
Mean $\pm$ SD	2.75 $\pm$ 0.53	209 $\pm$ 23	13.1 $\pm$ 3.6

Abbreviations: $V_{d_{ss}}$, volume of distribution at steady state; $T_{1/2\beta}$, elimination half-life.

Discussion

Age-related effects on pharmacokinetic processes are thought to occur in children because of developmental and maturational changes in body composition and organ function (9). Kinetic studies in infants and children have shown age-related changes in drug elimination of morphine, meperidine, and fentanyl (4,10,11). Our study examined the effect of age on sufentanil pharmacokinetics and pharmacodynamics in pediatric cardiovascular patients.

In this study, the pharmacokinetics of sufentanil were best described by a triexponential curve in all patients in the four groups. This finding is similar to the data of Bovill et al. (12), in which the pharma-

Table 3. Sufentanil Pharmacokinetic Values

Patient group	P (ng/ml)	π (min ⁻¹)	T _{1/2} π (min)	A (ng/ml)	α (min ⁻¹)	T _{1/2} α (min)	B (ng/ml)	β (min ⁻¹)	T _{1/2} β (min)
I	15.9 ± 9.8	0.51 ± 0.17	1.6 ± 0.8	3.8 ± 2.2	0.047 ± 0.032	23.4 ± 17.3	2.11 ± 0.94	0.0011 ± 0.0006	737 ^a ± 346
II	13.9 ± 15.9	0.59 ± 0.34	1.5 ± 0.8	4.1 ± 3.0	0.048 ± 0.017	15.8 ± 5.0	1.31 ± 0.47	0.0034 ± 0.001	214 ± 41
III	25.1 ± 20.5	0.56 ± 0.21	1.5 ± 0.87	6.7 ± 3.17	0.045 ± 0.020	19.6 ± 6.0	2.44 ± 0.60	0.0051 ± 0.001	140 ± 30
IV	19.6 ± 11.3	0.34 ± 0.17	2.6 ± 1.12	7.3 ± 1.8	0.043 ± 0.020	20.4 ± 5.9	2.37 ± 1.21	0.0033 ± 0.001	209 ± 23

All values expressed as mean ± SD.

^aP < 0.05 group I vs groups II, III, IV.Abbreviations: P, intercept of fast distribution half-life; π , slope of fast distribution half-life; T_{1/2} π , fast distribution half-life; A, intercept of slow distribution half-life; α , slope of slow distribution half-life; T_{1/2} α , slow distribution half-life; B, intercept of slow distribution half-life; β , slope of slow distribution half-life; T_{1/2} β , elimination half-life.

Table 4. Sufentanil Pharmacokinetic Values

Patient group	Vd _{ss} (L/kg)	Clearance (ml·kg ⁻¹ ·min ⁻¹)	K ₁₀ (min ⁻¹)	K ₁₂ (min ⁻¹)	K ₁₃ (min ⁻¹)	K ₂₁ (min ⁻¹)	K ₃₁ (min ⁻¹)
I	4.15 ^a ± 1.01	6.7 ^a ± 6.1	0.011 ± 0.007	0.279 ± 0.111	0.091 ± 0.059	0.159 ± 0.078	0.020 ± 0.015
II	3.09 ± 0.95	18.1 ^b ± 2.7	0.035 ± 0.020	0.315 ± 0.227	0.084 ± 0.050	0.190 ± 0.080	0.015 ± 0.004
III	2.73 ± 0.50	16.9 ^b ± 2.2	0.043 ± 0.020	0.290 ± 0.130	0.060 ± 0.042	0.196 ± 0.098	0.016 ± 0.005
IV	2.75 ± 0.53	13.1 ± 0.4	0.032 ± 0.012	0.157 ± 0.106	0.057 ± 0.039	0.130 ± 0.064	0.012 ± 0.004

All values are mean ± SD.

^aP < 0.05 group I vs groups II, III, IV.^bP < 0.05 groups II, III vs group IV.^cP < 0.05 group I vs groups III, IV.Abbreviations: Vd_{ss}, volume of distribution at steady state; K, intercompartment kinetic constant.

Table 5. Sufentanil Pharmacodynamics

Group	Plasma levels at anesthetic supplementation (ng/ml)
I	2.51 ± 0.64 ^a
II	1.58 ± 0.31
III	1.53 ± 0.35
IV	1.56 ± 0.40

All entries are mean ± SD.

^aP < 0.05 group I vs groups II, III, IV.

cokinetics of sufentanil were described by a triexponential model in adult patients undergoing surgery. Davis et al. (13), in a study of the pediatric population, described a two-compartment model for sufentanil elimination. Because the sampling interval in their study was limited to only 120 min, we believe that the study design determined the biexponential modelling of the sufentanil concentrations, resulting in inconclusive kinetic data. In our study, the sampling period was 1200 min in 21 patients; in the remaining 7 patients this period was between 240 and 300 min. This extended sampling period permitted better determination of sufentanil decay based on patient characteristics rather than study design.

The slow distribution half-life (T_{1/2} α) was nearly identical in all groups, and similar to the kinetic data of Bovill et al. in adult patients (12). We conclude that there are no age-related changes in the rate of uptake of sufentanil into well perfused tissues, and these data

are in keeping with the highly lipophilic nature of this drug.

The Vd_{ss} in our patients was much greater than total body water. This finding is consistent with the reported high tissue and protein binding of the drug and consistent with the findings of Bovill et al. in adult surgical patients (12). The neonatal group had significantly larger Vd_{ss} (4.15 L/kg) when compared with the other groups. This finding suggests that the changes in Vd_{ss} for sufentanil may be age-related. Similar findings of a larger Vd_{ss} in young patients have been reported for other lipophilic compounds such as fentanyl, meperidine, and diazepam, and are thought to be due to known age-related differences in body composition (4,11,14,15). On the other hand, the changes in Vd_{ss} may be a consequence of congenital heart disease and the selective presence of congestive heart failure in the neonates.

The total plasma clearance of sufentanil also showed changes between the different age groups. The clearance in our adolescent group was 13.1 ml·kg⁻¹·min⁻¹, which is nearly identical to the clearance reported for adult surgical patients (12.6 ml·kg⁻¹·min⁻¹) (12). Our infant and children groups had increased plasma clearance of sufentanil with rates of 18.1 and 16.9 ml·kg⁻¹·min⁻¹, respectively. This finding is consistent with the increased clearances reported in young patients for other drugs such as fentanyl, thiopental, edrophonium, and ketamine (3,16,17,18). Of note, however, is the marked decrease in clearance (6.7

$\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) in our patients younger than 1 month. Similar observations have been reported for fentanyl in neonatal kinetic studies (4). We speculate that our findings may have two explanations. First, because sufentanil is primarily metabolized by oxidative demethylation in the liver, the delayed maturation of these microsomal enzymes reported in neonates may have decreased the clearance rates (19). Alternatively, because sufentanil is reported to have a high intrinsic clearance, hepatic elimination will be sensitive to changes in liver blood flow (12). The specific cardiovascular disease states in our patients may have had a greater effect on hepatic blood flow in the neonatal group in a manner that was not predictable, thus contributing to the decreased clearance rates observed.

The half-life of the terminal elimination phase ($T_{1/2\beta}$) for sufentanil was similar in infants, children, and adolescents (groups II, III, and IV, respectively). The mean $T_{1/2\beta}$ in these patients was 187 ± 31 min, and corresponds with the $T_{1/2\beta}$ value of 164 ± 69 min reported in adult surgical patients (11). Of interest, the $T_{1/2\beta}$ in the neonatal group was three times greater than that of the other groups in our study. This delayed elimination is a result of the larger V_{dss} observed in the neonatal group, which results in a longer $T_{1/2\beta}$ for any given clearance.

We believe the observation of a greater variability of the pharmacokinetic parameters for sufentanil in the neonatal group is important. Because the hepatic maturational process is accelerated, variably induced, and unpredictable in the first month of life, large variations in drug disposition are to be expected (20,21). Our data supports this hypothesis. Changing hepatic function affects drug metabolism and disposition, making predictable dosing in the neonatal period very difficult. Therefore, we believe that the risk of overdosing or underdosing sufentanil is increased in the neonatal period.

The doses of sufentanil used in this study provided initial hemodynamic stability in all patients except one neonate who required temporary chronotropic and inotropic support for severe bradycardia and hypotension after sufentanil administration. All the patients in groups II–IV and one patient in group I required supplemental anesthesia intraoperatively. This observation suggests a limited role for sufentanil as a sole, one-time bolus anesthetic agent during pediatric cardiovascular surgery, which is consistent with the findings in the study of Moore et al. (2).

Observations of age-related differences in pharmacodynamics at similar points of hemodynamic and/or patient responsiveness revealed a higher plasma concentration of sufentanil in the neonatal group compared with the other groups. Because none of the

patients in group I received premedication, persistent effects of premedicant drugs in groups II, III, and IV may have reduced the concentration of sufentanil required to suppress sympathetic-hemodynamic responsiveness to surgical stimulation. Alternatively, this finding may suggest that neonates have a decreased sensitivity to the anesthetic effects of sufentanil or, less likely, that acute tolerance is developed.

In conclusion, we have described the pharmacokinetics of sufentanil in pediatric patients undergoing cardiovascular surgery. We have demonstrated that sufentanil has pharmacokinetic properties that may be age-related. However, all of our patients had cardiovascular disease that may have affected the observed differences in pharmacokinetics. Because our study design did not include a control group of normal healthy neonates, infants, children, and adolescents, the question of age-related vs disease-related differences in sufentanil kinetics cannot be definitively answered. Nonetheless, this study was performed under actual clinical situations with the usual anesthetic doses of sufentanil. Extrapolation of this kinetic data to other clinical situations may apply, although evaluation of their direct effect on pharmacokinetic processes is required.

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Effects of Isoflurane on Myocardial Blood Flow, Function, and Oxygen Consumption in the Presence of Critical Coronary Stenosis in Dogs

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TATEKAWA S, TRABER KB, HANTLER CB, TAIT AR, GALLAGHER KP, KNIGHT PR. Effects of isoflurane on myocardial blood flow, function, and oxygen consumption in the presence of critical coronary stenosis in dogs. *Anesth Analg* 1987;66:1073-82.

Because isoflurane has been reported to produce coronary steal, we studied 12 open chest, anesthetized (pentobarbital) dogs with critical stenosis (CS) of the left circumflex coronary artery (LCA). Sonomicrometers were implanted to measure systolic wall thickening, myocardial blood flow (MBF) was measured with microspheres (15 μ m diameter), and regional venous sampling was performed to estimate regional oxygen extraction and myocardial oxygen consumption (MVO₂). Anesthetic concentrations of isoflurane reduced arterial blood pressure dramatically, resulting in a maldistribution of MBF distal to the CS consistent with the pattern characterizing a transmural coronary steal effect. Elevation of arterial blood pressure with phenylephrine during high concentration isoflurane ($1.7 \pm 0.1\%$) augmented

MBF, but the maldistribution distal to the CS persisted. Despite the maldistribution, however, there was no indication of ischemia in the LCA region because systolic wall thickening, oxygen extraction, and MVO₂ were not significantly different between the LCA and left anterior descending coronary artery (LAD) (control) areas. Because wall thickening, oxygen extraction, and MVO₂ were markedly reduced by isoflurane in both the LCA and control areas, it was concluded that isoflurane substantially reduced myocardial oxygen requirements by inducing myocardial depression, reducing heart rate, and decreasing afterload. Consequently, the apparent maldistribution of LCA blood flow (coronary steal) was due to the hemodynamic and vasodilatory effects of isoflurane, but did not result in ischemia because the level of blood flow was at or above the requirements of the myocardium.

Key Words: ANESTHETICS, VOLATILE—*isoflurane*.
HEART, BLOOD FLOW—*myocardial*.

Isoflurane is an inhalation anesthetic that produces systemic vasodilation but reportedly preserves myocardial contractile performance (1,2). It is advantageous as an inhalation anesthetic in patients having carotid endarterectomy because it decreases cerebral electrical activity and cerebral oxygen consumption (3), thereby affording cerebral protection by reducing the requirement for oxygen (4). However, the potent

vasodilatory properties of isoflurane often reduce systemic blood pressure. To maintain cerebral blood flow at acceptable levels during these procedures, vasopressors such as phenylephrine are infused.

Although the combination of isoflurane and phenylephrine may be beneficial for the supply/demand relation of the brain, recent evidence suggests this combination may be detrimental to the heart. Isoflurane alone may induce myocardial lactate production or produce myocardial wall motion abnormalities in vascular and coronary arterial bypass procedures (5-8) and may produce coronary steal in an animal preparation (9,10). These effects contrast with those of halothane (10,11), and suggest that isoflurane may produce myocardial ischemia in the presence of coronary artery disease.

The purpose of the present study was to examine the effects of isoflurane alone and in combination with phenylephrine on regional myocardial blood flow (MBF) distribution, myocardial contractile function, oxygen extraction, and myocardial oxygen consumption.

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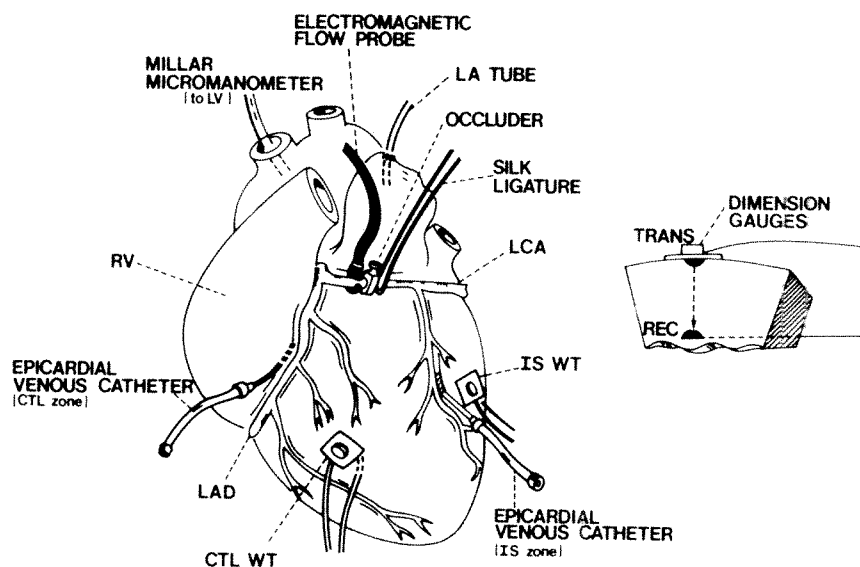


Figure 1. Diagram of instrumentation used in the canine open chest preparation of this study. Ultrasonic crystals measuring myocardial wall thickening were placed in the control region (CTL WT) supplied by the left anterior descending artery (LAD) and the stenotic region (IS WT) supplied by the left circumflex artery (LCA). The inset on the right depicts a cross-section of myocardium with transmitting (TRANS) crystal on the epicardium and the receiving crystal (REC) in the subendocardium.

tion (MVO_2) in the presence of experimental critical coronary stenosis. Critical coronary stenosis (CS), defined as the degree of obstruction that nearly eliminates the reactive hyperemic response without changing mean coronary blood flow, corresponds to a reduction in diameter of approximately 70–80% (12–14). With CS, subendocardial flow reserve is nearly exhausted but the subepicardial layers are capable of additional vasodilation, a set of conditions predisposing to transmural coronary steal. We hypothesized that isoflurane could produce a transmural steal phenomenon by reducing perfusion pressure and that this would result in ischemia, which could be defined in terms of mechanical dysfunction and increased oxygen extraction (12,13).

Methods

Twelve mongrel dogs of both sexes, weighing between 22 and 28 kg, were anesthetized with sodium pentobarbital (35–40 mg/kg IV), intubated with a cuffed endotracheal tube, and ventilated with an Air Shield Ventimeter Controller (VC 20-1). Supplemental oxygen was administered to maintain $\text{PaCO}_2 > 100$ mm Hg and PaO_2 between 35 and 42 mm Hg. During the surgical preparation, pentobarbital was infused intermittently (not over 50 mg/hr) with the last bolus dose given 30 min before the start of the experiment. Pentobarbital anesthesia was maintained at an infusion rate of $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ throughout the experimental period. A constant infusion of lactated Ringer's solution or normal saline (0.9%) was administered IV to maintain left atrial pressure (LAP) between 5 and 10 mm Hg. The left femoral and right carotid

arteries were catheterized with Tygon (0.04 mm inner diameter) tubing for simultaneous withdrawal of arterial samples during microsphere injection.

Arterial blood pressure was measured with a Statham P23Db transducer connected to a catheter inserted into the right femoral artery. A pulmonary artery thermodilution catheter was inserted through the right external jugular vein to measure cardiac output (CO), determined in triplicate by thermodilution using 5 ml of ice-cold normal saline injected into the right atrium. The injectate was administered through the standard port of a Swan-Ganz catheter, the proper location of which was verified at necropsy. To measure left ventricular pressure, a Millar high fidelity micromanometer (model PC350) was passed into the left ventricle via the carotid artery and aorta. The left ventricular pressure signal was differentiated to continuously measure dp/dt .

Coronary Flow Measurement and Critical Coronary Stenosis

A left thoracotomy was performed through the fifth or sixth intercostal space. The pericardium was incised, and the heart was suspended in a pericardial cradle. A Tygon (0.04 mm inner diameter) catheter was placed in the left atrium to measure LAP and inject microspheres. The proximal left circumflex coronary artery (LCA) was dissected free and an electromagnetic flow probe was placed around it to measure coronary blood flow (with a Biotronex Laboratories Pulsed-Logic Flow Meter, Model BL610). A plastic screw clamp, placed distal to the flow probe, was used to partially narrow the coronary artery to obtain CS.

A 2.0 silk ligature was placed loosely around the circumflex artery to produce temporary (5 sec) complete occlusions for production of reactive hyperemic responses. Critical stenosis was defined as the degree of obstruction that nearly eliminated the reactive hyperemic response after release of the occlusions without changing mean coronary blood flow (12-16).

Myocardial Blood Flow Measurements

Regional MBF was measured with tracer-labeled microspheres (15 μm in diameter, New England Nuclear) using the reference withdrawal method (17). Four injections were made in every experiment, using one of six available isotopes (^{141}Ce , ^{113}Sn , ^{51}Cr , ^{103}Ru , ^{95}Nb , ^{46}Sc) for each flow determination. The choice of isotope was determined by which isotopes were available at the time, and the order of their injection was randomized. To ensure adequate dispersal, microsphere suspensions were sonicated for a minimum of 30 min and vortexed for 5 min before injection into the left atrium. Approximately 1-2 million microspheres were injected into the left atrium for measuring blood flows. Reference arterial samples were obtained simultaneously from both femoral and carotid arteries at a constant rate (7.0 ml/min) with a Harvard withdrawal pump; withdrawals were initiated before injection of the microspheres and completed 2 min later.

At the end of the experiments, the dogs were killed with intravenous KCl. The heart was removed and placed in formalin for sectioning. Multiple full thickness sections were obtained in a standardized fashion around complete rings of the left ventricle. Each block of tissue was divided into three pieces of approximately equal thickness from the endocardium to epicardium. Papillary muscles were discarded. The tissue samples were weighed and placed in counting vials for assay of radioactivity in a Tracor (model 1185) gamma scintillation counter. After correcting the counts in each tissue sample for background and overlapping counts with simultaneous equations, blood flow was calculated with the equation (17): $Q_m = (C_m \times Q_r)/C_r$, where Q_m = myocardial blood flow (ml/min), C_m = counts/min in tissue samples, Q_r = withdrawal rate of the reference arterial sample (ml/min), and C_r = counts/min in the reference arterial sample. Flow per gram of tissue was calculated by dividing flow by the weight of the appropriate sample. Background and overlap corrections and blood flow calculations were performed on an Apple IIe microcomputer. To standardize the data analysis, the posterior papillary muscle tissue samples (perfused by the LCA) were designated as the stenotic zone, and the anterior wall

and anterior papillary muscle tissue samples (perfused by the left anterior descending coronary artery) were designated as representing the control zone.

Regional Myocardial Function

Regional myocardial function was measured with sonomicrometers arrayed to measure transmural wall thickness (18,19). Two pairs of ultrasonic crystals were implanted as depicted in Figure 1. One pair was located within the area supplied by the LCA (stenotic region), the other in the area of myocardium supplied by the LAD (control region). As shown in the inset of Figure 1, one crystal of each wall thickness pair was in the endocardium (2-mm diameter) and the other crystal was attached to the epicardium (4-mm diameter) over the position of the inner crystal. The inner crystal was inserted tangentially through the myocardium to the subendocardium. The epicardial crystal, attached to a Dacron patch, was sutured to the epicardial surface over the position of the subendocardial crystal after locating the position of least distance between the crystals while monitoring the signals with an oscilloscope (19). The position of the crystals was carefully examined at the time of necropsy to verify correct alignment, following our usual criteria (20).

Regional Myocardial Oxygen Consumption

In five of the dogs, 22-gauge, 2-cm catheters (Deseret Medical Laboratory intravenous catheter with "Y" adapter) were inserted into an epicardial vein in the regions supplied by the LAD (control zone) and the LCA (stenotic zone) as shown in Figure 1. The catheters were flushed and capped. The dogs were systemically heparinized with 3000 U heparin. At each data collection point, 1-ml samples were obtained from each epicardial venous catheter and from the arterial line by spontaneous flow (without aspiration) under mineral oil to prevent ambient oxygen contamination for determination of hemoglobin concentration and oxygen content (Instrument Laboratories Co-oximeter IL 282). Regional MVO_2 was calculated using the Fick principle (arterial oxygen content - venous oxygen content) $\times$ regional transmural blood flow. Regional transmural blood flow was calculated by averaging the subendocardial, midmyocardial, and subepicardial blood flow in the stenotic zone (posterior papillary muscle samples) and the control zone (mean of the anterior and anterior papillary muscle samples). Percent oxygen extraction was calculated as (arterial oxygen content - regional venous oxygen content)/arterial oxygen content $\times$ 100.

Table 1. Hemodynamic Data

	Baseline	Isoflurane 0.7%	P	End point isoflurane	P	End point isoflurane and phenylephrine
HR	154 ± 5	136 ± 5 ^a	+	109 ± 4 ^a	NS	106 ± 4 ^a
SAP	178 ± 3	141 ± 4 ^a	+	101 ± 2 ^a	+	142 ± 3 ^a
DAP	131 ± 4	101 ± 5 ^a	+	69 ± 3 ^a	+	99 ± 3 ^a
MAP	148 ± 3	115 ± 5 ^a	+	80 ± 2 ^a	+	114 ± 3 ^a
LAP	6.9 ± 1.0	5.6 ± 0.9 ^a	NS	6.8 ± 1.0	+	12.1 ± 1.5 ^a
SVR	2524 ± 217	2359 ± 235	NS	1980 ± 208 ^a	NS	2740 ± 157
CO	4.9 ± 0.3	4.12 ± 0.16 ^a	+	3.39 ± 0.26 ^a	+	3.26 ± 0.15 ^a
Percent of peak positive dP/dt	100	69.3 ± 3.0 ^a	NS	41.8 ± 2.5 ^a	+	51.9 ± 2.9 ^a

Values are mean ± SE

Abbreviations: HR, heart rate (beats/min); SAP, systolic arterial pressure (mm Hg); DAP, diastolic arterial pressure (mm Hg); MAP, mean arterial pressure (mm Hg); LAP, left atrial pressure (mm Hg); SVR, systemic vascular resistance (dynes·sec⁻¹·cm⁻⁵); CO, cardiac output (L/min); +, *P* < 0.05 between groups; NS, not significant.^a*P* < 0.05 compared with baseline

Experimental Protocol

Thirty minutes to 1 hr were allowed for the dog to stabilize after the completion of instrumentation. While recording baseline hemodynamic and dimension measurements, a baseline injection of microspheres was performed. In five experiments, baseline samples were obtained for determination of regional MVO_2 and oxygen extraction. Hemodynamic, dimensional, and metabolic measurements were obtained at each microsphere injection point. Isoflurane was then administered to an end-tidal concentration of 0.7% (determined with mass spectrometry) for 20 min and a second microsphere injection was made. The concentration of isoflurane was then increased until a systolic blood pressure of approximately 100 mm Hg was obtained, and this was designated the end point isoflurane concentration. After conditions stabilized a third injection of microspheres was made. Next phenylephrine ($0.5\text{--}0.8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was infused in an amount adequate to increase systolic arterial pressure to the level observed when the isoflurane concentration was 0.7%. A fourth microsphere injection was made when stable conditions were reestablished.

Data Analysis

Recordings were made during each experiment on a six-channel pressurized-ink recorder (Gould model 2600). Variables analyzed were heart rate, systolic and diastolic arterial pressure, MAP, LAP, CO, regional MBF, wall thickness at end diastole (identified as the point corresponding to the onset of the positive dP/dt signal) and end systole (defined as the point 20 msec before peak negative dP/dt), and extent of wall thickening. The extent of wall thickening was calculated as the difference in millimeters between end-diastolic and end-systolic wall thickness. Dimensional and

hemodynamic data were analyzed from recordings made at 100 mm/sec by averaging at least five cardiac cycles. Results are expressed in text, tables, and figures as mean ± SEM.

Hemodynamic, metabolic, MBF, and dimensional data were analyzed at four time periods (baseline, 0.7% isoflurane, end point isoflurane concentration, and end point isoflurane plus phenylephrine) with analysis of variance. When significant *F* values were detected, paired *t*-tests were performed to distinguish which time periods differed from one another. Because multiple comparisons were performed, the Bonferroni inequality adjustment was used to correct the acceptable α -level for the number of comparisons (21). A probability level of *P* < 0.05 (appropriately corrected with the Bonferroni inequality adjustment) was considered statistically significant. Unpaired *t*-tests were used to compare wall thickness variables and blood flow data in two locations: 1) control zone (LAD region) and 2) stenotic zone (LCA region).

Exclusion of Data

A total of 16 dogs were studied, 12 of which were included in this report. One of the dogs was excluded because of evidence from the blood flow data of possible ischemia before the introduction of isoflurane. The endo/epi ratio was reversed, suggesting that a hypercritical stenosis of the LCA had been produced. Another dog was excluded because it developed extreme, prolonged hypotension after the initial injection of microspheres. A third dog was excluded because of inability to use the microsphere data, possibly because of poor mixing, indicated by unsatisfactory matching of radioactive counts in the two reference blood samples. A fourth dog was excluded because of evidence of *Dirofilaria* at necropsy.

Table 2. Regional Myocardial Blood Flow ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$) Data

	Baseline	Isoflurane 0.7%	P	End point isoflurane	P	End point isoflurane and phenylephrine
Control region (LAD)						
Endo	2.16 ± 0.18	1.73 ± 0.16	+	1.81 ± 0.20	+	3.98 ± 0.65
Mid	2.16 ± 0.19	1.64 ± 0.12	NS	1.77 ± 0.21	+	3.80 ± 0.57
Epi	2.02 ± 0.20	1.58 ± 0.12	NS	1.58 ± 0.16	+	2.87 ± 0.34
Endo/epi	1.10 ± 0.06	1.09 ± 0.06	NS	1.15 ± 0.08	NS	1.37 ± 0.11
Stenotic region (LCA)						
Endo	2.41 ± 0.22	$1.58 \pm 0.14^*$	+	$0.90 \pm 0.15^*$	+	1.83 ± 0.27
Mid	2.34 ± 0.22	$1.76 \pm 0.13^*$	NS	$1.26 \pm 0.18^*$	+	2.57 ± 0.32
Epi	1.98 ± 0.20	1.65 ± 0.11	NS	1.54 ± 0.18	+	3.09 ± 0.35
Endo/epi	1.24 ± 0.06	$0.98 \pm 0.07^*$	+	$0.61 \pm 0.08^*$	NS	$0.59 \pm 0.05^*$

Values are mean $\pm$ SE

Abbreviations: Endo, subendocardial blood flow; Mid, midmyocardial blood flow; Epi, subepicardial blood flow; Endo/epi, ratio of subendocardial blood flow to subepicardial blood flow; +, $P < 0.05$ between groups; NS, not significant.

* $P < 0.05$ compared with baseline.

Results

Hemodynamic data are summarized in Table 1. Before isoflurane administration, the dogs were anesthetized with pentobarbital. Regional MBF, summarized in Table 2, was relatively high, consistent with the somewhat hyperdynamic baseline conditions (Table 1). As shown in Figure 2, there were no significant differences in MBF between the LAD (control) and LCA (stenotic) regions during baseline conditions. A normal transmural pattern of perfusion was evident in the myocardium perfused by the LCA. The endo/epi ratio was >1 during baseline conditions and was not significantly different from the baseline endo/epi ratio in the control area, demonstrating that we had successfully produced a CS that nearly eliminated the reactive hyperemic response but did so without altering baseline perfusion.

Percentage systolic wall thickening was $25.5 \pm 2.4\%$ in the LAD region and $20.8 \pm 1.7\%$ in the LCA region (Table 3). Representative recordings of wall thickening waveforms are presented in Figure 3. To standardize the change in wall thickening between regions with isoflurane administration, in Figure 4 the data are presented as relative changes in wall thickening from baseline.

In five dogs, regional MVO_2 and oxygen extraction were also determined. There were no significant differences in hemodynamics, MBF, and regional contractile function in the first seven dogs compared with the last five. Reflecting the relatively hyperdynamic baseline state, regional MVO_2 was high, averaging $24.2 \pm 4.8 \text{ ml O}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ in the LCA region and $23.4 \pm 6.2 \text{ ml O}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ in the LAD region. Regional oxygen extraction was similar between the two zones, averaging $62.3 \pm 1.3\%$ in the LCA region and $63.2 \pm 2.2\%$ in the area perfused by the

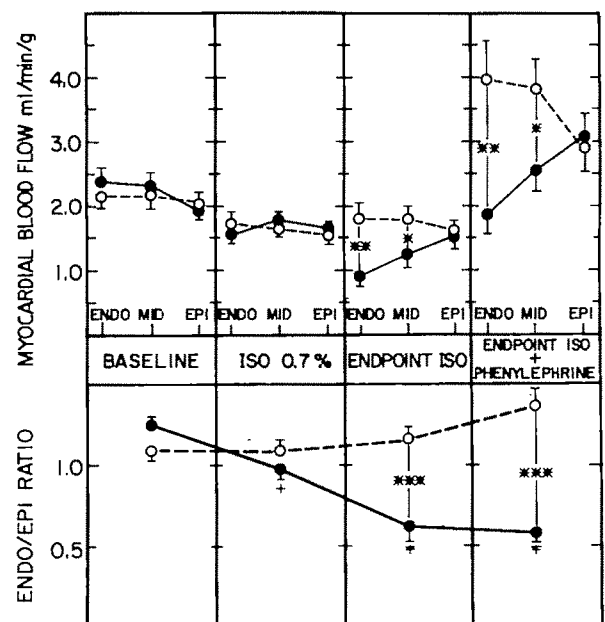


Figure 2. Myocardial blood flow in tissue samples in the control region supplied by the left anterior descending region (○---○) and the stenotic region supplied by the left circumflex artery (●---●). Blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$) is shown in three layers across the ventricular wall from subendocardium (ENDO), midmyocardium (MID) to subepicardium (EPI) at baseline, isoflurane 0.7% (ISO 0.7%), end point isoflurane concentration (ENDPOINT ISO), and end point isoflurane concentration plus phenylephrine (ENDPOINT ISO + PHENYLEPHRINE). The endocardial to epicardial blood flow ratio (ENDO/EPI RATIO) is shown in the graph below. * $P < 0.05$; ** $P < 0.005$; *** $P < 0.0005$; + $P < 0.005$ compared with baseline; † $P < 0.0005$ compared with baseline.

LAD. Thus, there was no difference in regional blood flow, contractile function, MVO_2 or oxygen extraction, demonstrating that during baseline conditions the CS did not adversely affect contractile performance or oxygen metabolism.

Table 3. Summary of Wall Thickening Data

	Baseline	Isoflurane 0.7%	P	End point isoflurane	P	End point isoflurane and phenylephrine
EDWTh (mm)						
Control	11.9 ± 0.5	12.0 ± 0.5	NS	12.2 ± 0.5	NS	12.0 ± 0.5
Stenotic	11.6 ± 0.5	11.7 ± 0.4	NS	11.6 ± 0.5	+	11.4 ± 0.5
ESWTh (mm)						
Control	14.5 ± 0.6	14.3 ± 0.6	NS	14.0 ± 0.5	NS	13.8 ± 0.5*
Stenotic	13.8 ± 0.5	13.7 ± 0.5	+	13.1 ± 0.4*	NS	12.9 ± 0.4*
ΔdWTh (mm)						
Control	2.97 ± 0.22	2.71 ± 0.21	+	2.15 ± 0.20*	NS	2.03 ± 0.23*
Stenotic	2.36 ± 0.17	2.04 ± 0.18*	+	1.47 ± 0.22*	NS	1.52 ± 0.19*
%ΔdWTh						
Control	25.5 ± 2.4	23.2 ± 2.1	+	18.2 ± 1.9*	NS	17.5 ± 2.2*
Stenotic	20.8 ± 1.7	17.8 ± 1.7*	NS	13.2 ± 2.2*	NS	13.8 ± 2.0*

Values are mean ± SE

Abbreviations: EDWTh, end diastolic wall thickness; ESWTh, end systolic wall thickness; ΔdWTh = EDWTh; %ΔdWTh = (ΔdWTh/EDWTh) × 100; +, P < 0.05 between groups; NS, not significant.

*P < 0.05 compared with baseline

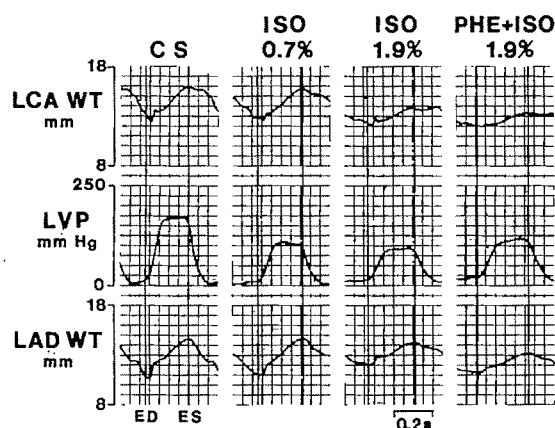


Figure 3. Representative recording of wall thickening waveforms during baseline conditions with critical stenosis (CS), isoflurane 0.7% (ISO 0.7%), end point isoflurane concentration (ISO 1.7%), and isoflurane 1.7% plus phenylephrine (ISO 1.7% + PHE). Wall thickening in the regions supplied by the left circumflex artery (LCA WT) and left anterior descending artery (LAD WT) was simultaneously measured along with left ventricular pressure (LVP) during isoflurane and phenylephrine administration. End-diastole (ED) and end-systole (ES) are indicated with the solid vertical lines.

With 0.7% isoflurane (equivalent to 0.5 MAC in the dog) administration, substantial hemodynamic alterations were observed. Heart rate and MAP decreased significantly (Table 1). Coincident with a rate-pressure product reduction of approximately 30% was a decrease in regional MBF (Table 2). Myocardial blood flow did not differ between the stenotic LCA region and the nonstenotic LAD region, but a significant reduction was noted in the endo/epi ratio of the LCA region (Fig. 2). Regional wall thickening decreased in both regions with 0.7% isoflurane, reflecting the global reduction in contractility indicated by a decrease in peak positive dP/dt of 31% ($P < 0.005$). Although the

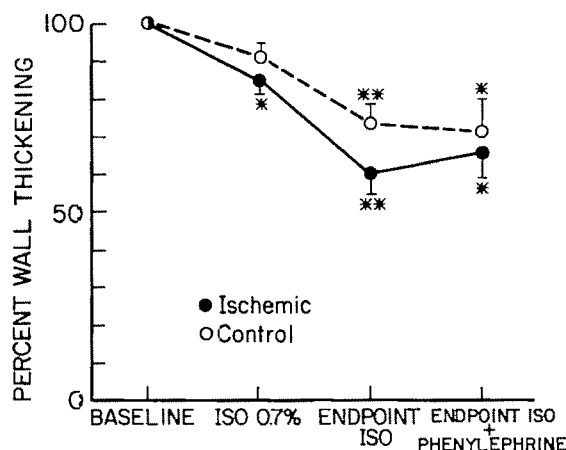
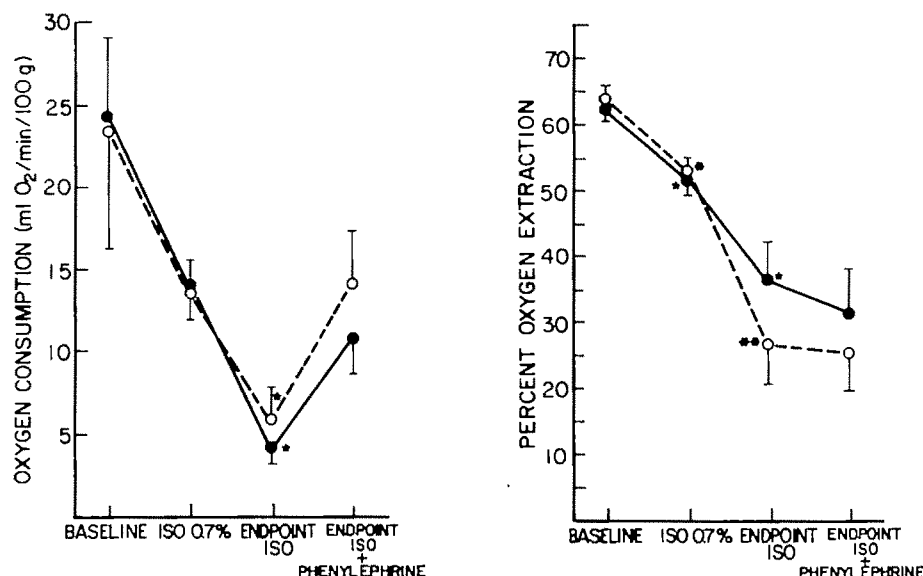


Figure 4. The percent changes in myocardial wall thickening from baseline to isoflurane 0.7% (ISO 0.7%), end point isoflurane concentration (ENDPOINT ISO), and end point isoflurane concentration plus phenylephrine (ENDPOINT ISO + PHENYLEPHRINE) are shown in the regions supplied by the left anterior descending artery (O--O) and the left circumflex artery (●--●) (* $P < 0.005$; ** $P < 0.0005$ compared with baseline).

relative changes in wall thickening were similar, a significant reduction in thickening (−14%) occurred only in the LCA region. In agreement with the changes in hemodynamic and dimensional parameters that suggested myocardial oxygen demand had been reduced, regional MVO_2 decreased 43% in the LCA region and 41% in the LAD region (Fig. 5). Regional oxygen extraction decreased 18% in the LCA region and 17% in the LAD region, indicating relative coronary vasodilation.

The end point isoflurane concentration (the concentration at which the systolic pressure was maintained at 100 mm Hg) was on the average $1.7 \pm 0.1\%$ (1.2 MAC for the dog). Along with the reduction in

Figure 5. Regional oxygen consumption and extraction in the region supplied by the left anterior descending artery (○--○) and the left circumflex artery (●--●) are depicted at baseline, isoflurane 0.7% (ISO 0.7%), end point isoflurane concentration (ENDPOINT ISO), and end point isoflurane concentration plus phenylephrine (ENDPOINT ISO + PHENYLEPHRINE). * $P < 0.05$, ** $P < 0.005$ compared with baseline.



MAP, increasing the isoflurane concentration induced a further reduction in heart rate, dP/dt , systemic vascular resistance (SVR), and CO (Table 1). The hemodynamic changes were associated with additional reduction in regional oxygen extraction indicative of greater coronary vasodilation (Fig. 5), an interpretation supported by the maintenance of myocardial blood flow in the nonstenotic LAD region at the same level observed at 0.7% isoflurane (Table 2) despite the decrease in myocardial work and oxygen consumption.

In the stenotic (LCA) region, however, a 63% reduction in subendocardial blood flow and 46% reduction in midmyocardial blood flow were observed (Table 2). The blood flow in the subepicardium was unchanged. Consequently, the endo/epi ratio decreased to 0.61 ± 0.08 , indicating a significant maldistribution of perfusion distal to the critical stenosis. Despite the reduced subendocardial blood flow in the stenotic region, myocardial wall thickening remained comparable in the two regions. As shown in Figure 4, there was a tendency for thickening in the LCA region to be reduced more than that in the LAD-supplied region. There was no significant difference, however, between the extent of thickening or percentage of thickening in the two areas, suggesting that each zone was characterized by similar levels of contractile performance. This was surprising given the marked disparity in blood flow distribution between the LAD and LCA-supplied zones.

With the administration of phenylephrine at the end point isoflurane concentration, MAP was restored to the level observed with 0.7% isoflurane (Table 1). In the nonstenotic LAD region, MBF increased

significantly and oxygen extraction remained low, suggesting that the high flows were due to coronary vasodilation and augmented perfusion pressure (Figure 5). In the stenotic LCA region, blood flows increased also but the maldistribution of myocardial blood flow persisted. The endo/epi ratio of 0.59 ± 0.05 observed with phenylephrine administration was not significantly different from the end point isoflurane value. Systolic wall thickening was not significantly changed and there was no significant difference between the stenotic and nonstenotic regions (Table 3). Likewise, there were no significant differences between MVO_2 and oxygen extraction in the two regions (Fig. 5).

Discussion

Recent evidence has accumulated suggesting that isoflurane predisposes patients with coronary artery disease to myocardial ischemia by inducing a maldistribution of coronary blood flow (coronary steal). In 1983, Sybert et al. suggested that isoflurane was a more potent coronary vasodilator than halothane or enflurane (22). That same year, Reiz et al. reported evidence of myocardial ischemia (ECG changes and decreased lactate extraction) in 10 of 21 patients undergoing major vascular surgery with isoflurane anesthesia (6). In 1985, Reiz and Ostman reported that during major vascular surgery seven of ten patients developed ST-segment changes and decreased lactate extraction that suggested the production of myocardial ischemia with the isoflurane-nitrous oxide anesthesia used in these patients (7). Moffitt et al.

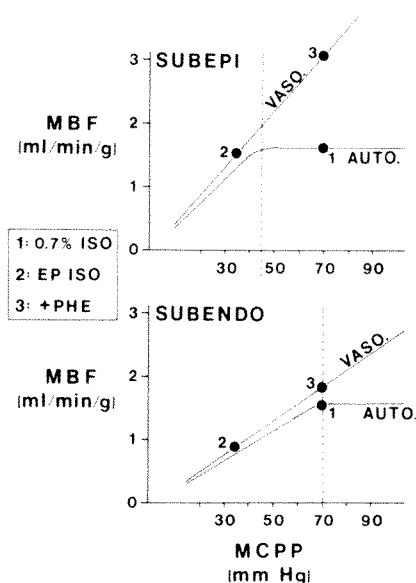


Figure 6. Hypothetical coronary pressure-flow curves used to propose an explanation for the alteration in the transmural pattern of myocardial blood flow (MBF) induced by isoflurane administration. Mean coronary perfusion pressure (MCP) distal to the critical stenosis is plotted on the x-axis assuming a pressure gradient of 45 mm Hg across the coronary narrowing. Autoregulating (AUTO) and maximally vasodilated (VASO) curves are shown. The dashed lines represent the inflexion points in the autoregulating curves of the subepicardium (SUBEPI, upper graph) and subendocardium (SUBENDO, lower graph), below which the autoregulating and vasodilated curves are nearly superimposable. The numbered points refer to the pressure-flow values at 0.7% isoflurane concentration (1, 0.7% ISO), end point isoflurane concentration (2, EP ISO), and end point concentrations plus phenylephrine (3, +PHE).

reported that lactate production occurred in three of ten patients studied during coronary artery surgery with isoflurane (8). They observed a 23% reduction in coronary resistance and a 56% increase in coronary sinus oxygen content, leading to the conclusion that myocardial ischemia with isoflurane was due to coronary steal.

The objective of this study was to examine the effects of isoflurane on MBF, contractile function, and MVO_2 in the setting of critical coronary stenosis in the dog, and to determine if the addition of phenylephrine to increase blood pressure improves MBF distribution. In the present study, isoflurane markedly reduced arterial blood pressure. Although decreased from 148 ± 3 to 80 ± 2 mm Hg at the end point isoflurane concentration, no significant change in the transmural distribution of MBF was observed in the region supplied by the nonstenotic LAD artery because 80 mm Hg is a level of pressure still within the autoregulatory range. However, in the area perfused by the critically stenosed LCA artery, the transmural pattern of blood flow was altered substantially, and

this pattern persisted even when blood pressure was elevated by phenylephrine (Fig. 2).

We believe the persistent maldistribution of blood flow in the LCA-supplied region can be explained in terms of the pressure-flow curves schematically shown in Figure 6. Depicted on the x-axis are hypothetical values of mean coronary perfusion pressure (MCP) based on an assumed pressure gradient across the coronary narrowing of 45 mm Hg (12,23). The blood flow values represent average data from Table 2 at an isoflurane concentration of 0.7% (0.7 ISO, point 1), end point concentration of isoflurane (EP ISO, point 2), and end point isoflurane plus phenylephrine administration (+PHE, point 3).

Critical stenosis is the degree of coronary narrowing that defines the point at which subendocardial flow reserve is nearly exhausted (12,13,15,18,23). Therefore, point 1 in the lower graph of Figure 6 is located near the inflexion point (shown with the vertical dashed line) of the autoregulating (AUTO) pressure-flow curve for the subendocardium. As demonstrated experimentally by Guyton et al. (24), blood flow will vary directly with changes in pressure below the knee in the curve, which is located at approximately 70 mm Hg of mean coronary perfusion pressure in the open chest dog. A further reduction in perfusion pressure would be expected to decrease subendocardial blood flow, which is what we observed when the concentration of isoflurane was augmented to the end point level (point 2, lower graph). Even though point 2 is located on the maximally vasodilated (VASO) pressure-flow curve, secondary to the strong vasodilatory effect of high-dose isoflurane, subendocardial blood flow remains low because the autoregulatory and vasodilated pressure-flow curves are nearly superimposable at pressures less than that at the knee of the autoregulatory curve (23).

In the subepicardium, the knee (dashed line, upper graph of Figure 6) of the autoregulating (AUTO) pressure-flow curve occurs at a lower perfusion pressure than in the subendocardium (11,12,23-25). The inflexion point in Figure 6 is depicted at a mean coronary perfusion pressure of 45 mm Hg, which represents the approximate value documented by Guyton et al. (24) below which subepicardial flow varies directly with perfusion pressure. Therefore, when blood pressure was reduced by increasing the isoflurane concentration from 0.7% (point 1) to the end point level (point 2), subepicardial blood flow did not decrease. An additional factor sustaining subepicardial blood flow may be that subepicardial perfusion was operating on a vasodilated (VASO) pressure-flow relation because of the high concentration of isoflurane (23). That substantial coronary vasodilation was

produced at the end point concentration of isoflurane is supported by the large reduction in coronary oxygen extraction we observed in five of the dogs (Fig. 5) and the maintenance of blood flow in the control (LAD) area despite the reduction in systemic blood pressure and myocardial oxygen demand.

When phenylephrine was infused, blood pressure returned to the level observed at the 0.7% isoflurane concentration. Given that the subepicardium was operating on linear, vasodilated pressure-flow curve, perfusion increased from point 2 to point 3 because pressure was elevated (upper graph, Fig. 6). The apparent maldistribution of transmural flow persisted, however, because subendocardial blood flow was restricted to the lower portion of its pressure-flow curve by the CS. Although phenylephrine restored subendocardial blood flow to the level observed with 0.7% isoflurane (Table 2), it did not increase as much as flow in the subepicardium, resulting in an endo/epi ratio that was unchanged compared with the end point concentration of isoflurane alone. Therefore, we conclude that the transmural coronary steal we observed with isoflurane is explicable in terms of hemodynamic changes. Although this conclusion is speculative, in that we did not measure distal coronary blood pressure, our interpretation is consistent with theoretical considerations (23) and experimental reports on the effects of other inhalation agents in the setting of critical stenosis (11,25).

Despite the maldistribution of blood flow in the myocardium supplied by the LCA, wall thickening in this area was not significantly different from wall thickening in the control area supplied by the LAD artery. Isoflurane exerted an equipotent myocardial depressant effect on wall thickening in both regions (Table 3, Figs. 3 and 4). Sustained wall thickening in the LCA supplied region is a startling finding suggesting that the maldistribution of blood flow was not associated with ischemia, in sharp contrast to previous studies demonstrating the sensitivity of wall thickening to reductions in myocardial perfusion (13,26).

One possible explanation for the apparent dissociation of MBF and function observed in the stenotic area was that myocardial demand did not remain constant with isoflurane administration. We hypothesize that isoflurane exerted a pronounced myocardial depressant effect and thereby reduced oxygen requirements, an effect amplified by decreased afterload and heart rate. Consequently, myocardial ischemia was not produced. The maldistribution of transmural blood flow, we propose, reflected the vasodilatory consequences of isoflurane administration rather than an ischemic pattern of perfusion. Superimposing iso-

flurane on barbiturate anesthesia may have minimally influenced the results we obtained. However, a constant infusion of barbiturate was necessary to maintain a light plane of anesthesia before and during the initial low concentrations of isoflurane. Even with this infusion, the dogs were mildly hyperdynamic (Table 1), suggestive of light anesthesia.

Previous work focusing on the correlation between subendocardial blood flow and myocardial function (wall thickening) was done during periods of increased myocardial demand (13-15). In contrast, the impact of isoflurane in our study was to reduce regional oxygen requirements. With isoflurane administration, MVO_2 decreased, on average, 63% below baseline levels, indicating that myocardial work had decreased substantially, a conclusion supported by the reductions in heart rate, peak left ventricular systolic pressure, and dP/dt (Table 1). To complement the regional MVO_2 data, which provide a measure of myocardial oxygen requirements, we also determined regional oxygen extraction. Oxygen extraction is high in the normal coronary circulation and changes in this parameter are tightly coupled to the adequacy of coronary blood flow. An increase in oxygen extraction reflects myocardial underperfusion, whereas a decrease implies that coronary vasodilation (not due to augmented myocardial work) is occurring. Oxygen extraction decreased 50% in our study without significant differences being evident between the normal LAD and stenotic LCA zones, which is consistent with the interpretation that isoflurane was exerting a substantial coronary vasodilatory effect. Thus, even though subendocardial blood flow was lower in the LCA than in the LAD region at the end point isoflurane concentration, we propose that the concomitant reduction in oxygen demand prevented the development of regional myocardial ischemia and dysfunction in the LCA-supplied myocardium. Phenylephrine administration increased myocardial perfusion and tended to increase MVO_2 but did not change the myocardial supply-demand situation.

Our findings appear to contrast with the recent study by Priebe and Foëx (27). Like us, they measured regional myocardial function with sonomicrometers in open chest dogs with coronary CS. Two levels of isoflurane were used to reduce arterial blood pressure to 70 and 55 mm Hg, which resulted in severe regional dysfunction in myocardium supplied by the critically stenosed artery. Priebe and Foëx (27) did not measure regional blood flow or oxygen metabolism, but their results are consistent with production of ischemia. Although apparently discrepant, we interpret the results of Priebe and Foëx to be consistent with our own in that they represent the consequences of a different

set of hemodynamic conditions. More profound hypotension was produced in their experiments than in ours, suggesting that the deleterious effects of inadequate perfusion pressure can overcome the beneficial effects of reduced myocardial oxygen demand.

In summary, isoflurane induced a maldistribution of MBF (transmural coronary steal) that persisted with phenylephrine administration in our canine model of critical coronary stenosis. However, myocardial functional ischemia was not observed. We conclude that isoflurane substantially reduced myocardial oxygen requirements such that the level of blood flow distal to the critical stenosis was adequate to meet the requirements of the myocardium. The apparent maldistribution of transmural blood flow was due to isoflurane-induced vasodilation in the outer muscle layers rather than ischemia.

Our results imply that isoflurane can be used safely in some patients with coronary artery disease. The potentially detrimental effects of transmural coronary steal produced by isoflurane-induced decreases in blood pressure were offset by isoflurane-induced reductions in determinants of myocardial oxygen demand. The balance between these opposing effects and the interaction of their balance with stenosis severity will dictate whether or not ischemia results with use of isoflurane. Therefore, preoperative assessment of the extent of coronary artery disease as well as careful intraoperative monitoring of cardiac status should be considered crucial when using isoflurane.

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The Effect of Nitrous Oxide on Cortical Cerebral Blood Flow during Anesthesia with Halothane and Isoflurane, with and without Morphine, in the Rabbit

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DRUMMOND JC, SCHELLER MS, TODD MM. The effect of nitrous oxide on cortical cerebral blood flow during anesthesia with halothane and isoflurane, with and without morphine, in the rabbit. *Anesth Analg* 1987;66:1083-9.

The effect of nitrous oxide on cortical cerebral blood flow (CBF) was examined during a varying background anesthetic state in the New Zealand White rabbit. Seventy percent nitrous oxide resulted in significant and similar increases in CBF during anesthesia with both 0.5 MAC of halothane (44 ± 14 to 63 ± 17 ml·100 g⁻¹·min⁻¹) (mean $\pm$ SD) and anesthesia with isoflurane (34 ± 9 to 41 ± 11 ml·100 g⁻¹·min⁻¹). During anesthesia with 1.0 MAC halothane or isoflurane, N₂O also increased CBF, but the increments (halothane, 73 ± 34 to 111 ± 54 ml·100 g⁻¹·min⁻¹; isoflurane 34 ± 13 to 69 ± 34 ml·100 g⁻¹·min⁻¹)

were significantly greater than those observed at 0.5 MAC. When 0.5 MAC halothane or isoflurane was supplemented with morphine (10 mg/kg followed by an infusion of 2 mg·kg⁻¹·min⁻¹), the CBF effect of N₂O was not significantly different from that observed with 0.5 MAC alone. It was concluded that, in the rabbit, the effects of N₂O on cortical CBF vary with the background anesthetic state and that the increase in CBF caused by N₂O becomes greater as the end-tidal concentration of halothane or isoflurane increases from 0.5 to 1.0 MAC. Morphine, when added to 0.5 MAC of halothane or isoflurane, does not alter the effect of 70% N₂O on cortical CBF.

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, VOLATILE—halothane, isoflurane. ANESTHETICS, INTRAVENOUS—morphine. BRAIN—blood flow.

A substantial body of data indicates that nitrous oxide increases cerebral blood flow (CBF) (1-7). The magnitude of this effect has varied considerably from study to study, but a recurring pattern among these investigations suggests that the production of deeper anesthesia may reduce the increase in CBF (or intracranial pressure [ICP] caused by the administration of N₂O (1,2,5,8). These observations led us to theorize that, in many instances, the N₂O-induced increases in CBF or ICP that have been reported were the product of an arousal or "second stage" phenomenon occurring when N₂O was administered to lightly anesthetized or unanesthetized subjects. The present study was undertaken to determine systematically whether the effect of N₂O on CBF is attenuated by deepening the

level of anesthesia by either increasing the concentration of a volatile agent (halothane or isoflurane) or by administration of a narcotic (morphine).

Methods

The protocol was reviewed and approved by the Animal Subjects Committee of the University of California, San Diego. Twelve New Zealand White rabbits of either sex, weighing 2.97 ± 0.12 kg (SD), and of approximate age 6 months were studied. The rabbits were assigned to one of two groups (halothane, isoflurane) on an alternating basis. Anesthesia was induced in a plexiglass box with the agent under study (4% halothane or 6% isoflurane) in oxygen. The animals were intubated, paralyzed with pancuronium 2 mg IV and mechanically ventilated (tidal volume, 15 ml/kg; rate, 20 breaths/min). Carbon dioxide was added to the inspired gas mixture to maintain normocarbica (PaCO₂ 38-42 mm Hg) throughout the study. End-tidal CO₂ concentration was monitored continuously (Beckman LB-II) throughout the experiment. Esophageal temperature was servocontrolled (heat lamp, warming pad) to 37.5°C.

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Table 1. Physiologic Data during Halothane Studies

	0.5 MAC		1.0 MAC		0.5 MAC/Morphine		RMANOVA
	N ₂	N ₂ O	N ₂	N ₂ O	N ₂	N ₂ O	
MAP (mm Hg)	78 ± 6	83 ± 7	76 ± 8	79 ± 7	85 ± 11	86 ± 16	NS
ICP (mm Hg)	0.3 ± 0.4	1.5 ± 1.2	1.1 ± 1.0	1.5 ± 0.8	0.7 ± 0.8	1.8 ± 0.9	<i>P</i> < 0.03
CBF (ml·100 g ⁻¹ ·min ⁻¹)	44 ± 14	63 ± 17 ^a	73 ± 34	111 ± 54 ^b	44 ± 6	54 ± 8 ^b	<i>P</i> < 0.0001
pH	7.35 ± 0.06	7.34 ± 0.04	7.35 ± 0.06	7.36 ± 0.04	7.34 ± 0.03	7.35 ± 0.03	NS
Paco ₂ (mm Hg)	39 ± 2	39 ± 1	40 ± 1	40 ± 2	39 ± 1	39 ± 1	NS
PaO ₂ (mm Hg)	94 ± 10	100 ± 17	105 ± 17	106 ± 19	101 ± 18	98 ± 22	NS

Values are mean ± SD.

Abbreviations: RMANOVA, repeated measures analysis of variance; MAP, mean arterial pressure; ICP, intracranial pressure; CBF, cerebral blood flow.

^a *P* < 0.001, for pairwise comparisons of CBF with and without N₂O.

^b *P* < 0.01 for pairwise comparisons of CBF with and without N₂O.

Anesthesia was maintained during surgical preparation with 0.75–1.0 MAC of halothane or isoflurane and 70% nitrous oxide. (MAC values for halothane and isoflurane are 1.39 and 2.05% (9), respectively. Throughout this communication the term "MAC" will be used to identify the concentration of the volatile agent without reference to the effect of any simultaneously administered nitrous oxide.) A catheter was placed in the abdominal aorta via the femoral artery for the recording of arterial pressure. The cranial preparation began simultaneously with the insertion of the vascular catheters. The cervical dura was exposed in the midline between the occiput and C-1 and a 19-gauge needle was passed through the atlantooccipital membrane for recording ICP. Blood pressure and ICP were referenced to the level of the external auditory meatus. The skull surface was exposed and platinum alloy needle electrodes (diameter 250 μm) were placed in the parietal cortex bilaterally for the recording of CBF by the hydrogen clearance method. The needles were positioned stereotactically via small burr holes to a depth of 2 mm. A silver-silver chloride reference electrode was placed subcutaneously over the mid-back.

Cerebral blood flow was determined intermittently using the hydrogen clearance technique (10–14) as previously employed in this laboratory (15,16). After saturation with 3–5% hydrogen, the hydrogen was omitted from the inspired gas mixture and the current between the platinum and the reference electrodes was recorded during the ensuing washout. Cerebral blood flow was calculated by the *T*_{1/2} method (10). The first 36 sec of the washout curve were discarded (13,14) to exclude from analysis the portion of the curve during which arterial hydrogen content was >5% of saturated levels (unpublished data from this laboratory). The CBF value for each determination was the arithmetic average of the two simultaneous parietal recordings. A single channel of bipolar EEG was re-

corded intermittently from subcutaneous fronto-occipital platinum electrodes (Grass).

The experimental phase of the study consisted of six CBF determinations in each rabbit. In both the halothane and isoflurane groups, studies were performed at 0.5 MAC, 1.0 MAC, and at 0.5 MAC supplemented with morphine administered in a bolus plus infusion regimen. Cerebral blood flow was recorded twice during each of these three background states, once in the presence of 70% N₂O and once in the presence of 70% nitrogen. The sequence of the 0.5 and 1.0 MAC studies was alternated so that in half the rabbits the 0.5 MAC determination was performed first and in half the 1.0 MAC study was first. The 0.5 MAC plus morphine studies were always performed last. The sequence of the N₂O and nitrogen exposures was varied systematically for all three background states such that half the time N₂O was studied first and half the time nitrogen was first. Angiotensin II was administered by infusion as required to maintain mean arterial pressure (MAP) greater than 65 mm Hg during 1.0 MAC administration.

At the conclusion of the surgical preparation, all wound margins were infiltrated with 0.25% bupivacaine. Noise in the experimental suite and contact with the animal were curtailed. The end-tidal concentrations of halothane or isoflurane were adjusted to the level appropriate to the first CBF determination (0.5 or 1.0 MAC) and a 45-min equilibration period ensued. The protocol was designed such that the period of administration before CBF determination for each of the two carrier gases (N₂ and N₂O) was standardized and constant at 15 min. Accordingly, if nitrogen was to be the carrier gas for the first CBF determination, then N₂O was administered during the equilibration period. At the conclusion of the equilibration period, 70% N₂O was replaced with 70% nitrogen and 15 min later the first CBF determination was performed. If the first flow determination was to

Table 2. Physiologic Data During Isoflurane Studies

	0.5 MAC		1.0 MAC		0.5 MAC/Morphine		RMANOVA
	N ₂	N ₂ O	N ₂	N ₂ O	N ₂	N ₂ O	
MAP (mm Hg)	86 ± 11	88 ± 11	80 ± 7	80 ± 5	83 ± 9	88 ± 13	NS
ICP (mm Hg)	0.9 ± 0.8	1.3 ± 0.9	1.2 ± 1.1	1.8 ± 1.2	1.0 ± 1.0	1.6 ± 1.2	NS
CBF (ml·100 g ⁻¹ ·min ⁻¹)	34 ± 9	41 ± 11*	34 ± 13	69 ± 34*	37 ± 11	52 ± 23	P < 0.0006
pH	7.37 ± 0.02	7.37 ± 0.01	7.39 ± 0.02	7.39 ± 0.03	7.37 ± 0.01	7.38 ± 0.04	NS
PaCO ₂ (mm Hg)	39 ± 2	39 ± 1	39 ± 1	39 ± 1	40 ± 2	40 ± 2	NS
PaO ₂ (mm Hg)	108 ± 53	104 ± 28	110 ± 42	101 ± 36	111 ± 41	101 ± 33	NS

Values are mean ± SD.

Abbreviations: RMANOVA, repeated measures analysis of variance; MAP, mean arterial pressure; ICP, intracranial pressure; CBF, cerebral blood flow.

*P < 0.005 for the pairwise comparisons of CBF with and without N₂O.

†P < 0.05 for the pairwise comparisons of CBF with and without N₂O.

be made with N₂O, then nitrogen was administered during the equilibration period and N₂O was introduced 15 min before CBF measurement. After the first CBF measurement, an N₂O-nitrogen exchange was made (end-tidal volatile agent concentration held constant) and the second CBF determination was made 15 min later.

For the third and fourth CBF determinations, the halothane or isoflurane end-tidal concentration was adjusted to the next MAC level (1.0 or 0.5). After 25 min at the new end-tidal level, the appropriate carrier gas was introduced and CBF determinations were made with N₂O and nitrogen at the same time intervals as described for the two measurements made at the initial MAC level.

The final two CBF determinations, the fifth and sixth, were made during the administration of 0.5 MAC of halothane or isoflurane supplemented with morphine sulphate. Immediately after the fourth CBF measurement, morphine sulphate, 10 mg/kg IV, was administered as a slow bolus, and an infusion of morphine was begun at a rate of 2 mg·kg⁻¹·hr⁻¹. Simultaneously, the end-tidal concentration of inhalation anesthetic was adjusted to the 0.5 MAC level and was maintained at that level for 25 min. The appropriate carrier gas, N₂O or nitrogen, was then introduced and 15 min later CBF was measured. Immediately thereafter, a nitrous oxide-nitrogen exchange was made, and the final CBF determination was made 15 min later.

Within each group the data were analyzed using a repeated measures analysis of variance (BMDP Statistical Software, University of California Press, Los Angeles, California, 1983). Where significant (*P* < 0.05) differences were identified, pairwise comparisons were performed using Student's *t*-test for paired data with the Bonferroni correction for multiple comparisons. Comparisons performed between groups were accomplished with a one-way analysis of variance. Statistical significance was assumed where *P* was < 0.05.

Results

The data are presented in Table 1 (halothane studies) and Table 2 (isoflurane studies). Mean arterial pressure PaCO₂, PaO₂, and pH did not vary significantly within or between groups. Angiotensin was rarely required and the dose employed never exceeded 0.18 μg·kg⁻¹·min⁻¹.

In every instance, in both the halothane and the isoflurane groups, and with all three background anesthetic conditions (0.5 MAC, 1.0 MAC, and 0.5 MAC with morphine sulphate), CBF was greater with 70% N₂O than with 70% nitrogen. In both the halothane and isoflurane groups, the increase in CBF associated with N₂O was significantly greater at 1.0 MAC than at 0.5 MAC. For individual rabbits, the increase in CBF at 1.0 MAC was always greater than that observed at 0.5 MAC. However, the degree to which the CBF increase at 1.0 MAC exceeded that at 0.5 MAC was quite variable, ranging in the halothane group from 2 to 47 ml·100 g⁻¹·min⁻¹ and in the isoflurane group from 3 to 75 ml·100 g⁻¹·min⁻¹. The increases in CBF did not differ between the 0.5 MAC and the 0.5 MAC/morphine states. Although there was an apparent trend toward an increase in ICP with the administration of N₂O, the differences were not statistically significant.

Cerebral blood flow was significantly greater during administration of 1.0 MAC halothane/70% nitrogen than during 1.0 MAC isoflurane/70% nitrogen: 73 ± 34 with halothane vs 34 ± 13 ml·100 g⁻¹·min⁻¹ with isoflurane. However, the increases in CBF that occurred when nitrogen was replaced with 70% N₂O did not differ: 38 ± 22 ml·100 g⁻¹·min⁻¹ for 1.0 MAC halothane and 36 ± 29 ml·100 g⁻¹·min⁻¹ for 1.0 MAC isoflurane.

Figure 1 presents an example of the frontooccipital cortical EEG recorded in one rabbit during isoflurane anesthesia with and without nitrous oxide. The changes observed during 1.0 MAC isoflurane anesthesia were

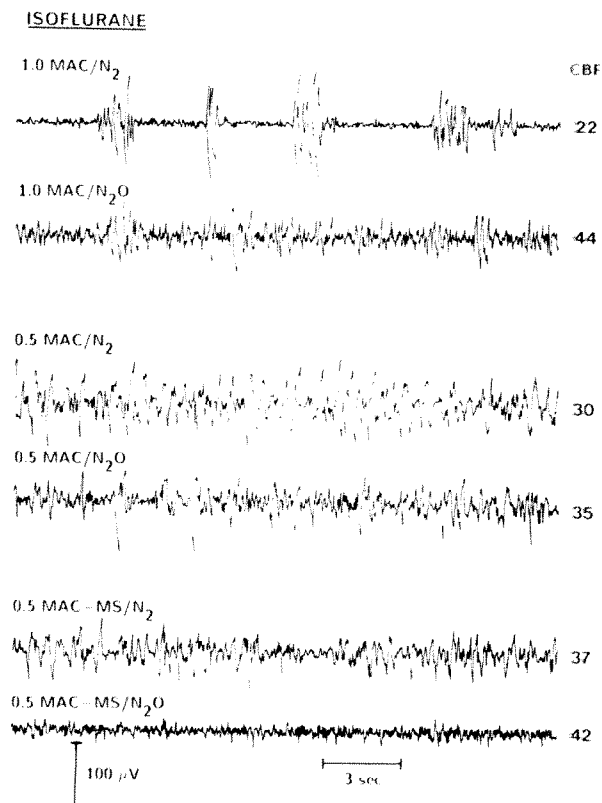


Figure 1. Frontooccipital EEG recorded during the six phases of study (0.5 MAC with and without N_2O , 1.0 MAC with and without N_2O , 0.5 MAC plus morphine with and without N_2O) in a rabbit that received isoflurane. The six CBF determinations (in $ml \cdot 100 g^{-1} \cdot min^{-1}$) made in this rabbit are presented at the right.

the most conspicuous and consistent in either group. One MAC isoflurane with 70% nitrogen consistently yielded a pattern characterized by spontaneous bursts of activity of intermediate frequency (7–9 Hz) and high amplitude separated by variable periods of activity of higher frequency (8–13 Hz) and very low amplitude. When nitrogen was replaced with 70% N_2O , this pattern invariably gave way to one characterized by continuous activity of 7–9 Hz and intermediate amplitude. The changes observed in the 0.5 MAC and 0.5 MAC/morphine studies were more subtle and less consistent. When apparent, the changes that occurred when nitrogen was replaced by N_2O were characterized by a decrease in slow wave activity, an increase in high frequency activity and occasionally an overall decrease in amplitude.

Figure 2 presents representative segments of the EEG recorded during the six phases of study in one of the rabbits given halothane. The general pattern of EEG alteration with all three background anesthetic states (1.0 MAC, 0.5 MAC, and 0.5 MAC/morphine) was one of an overall decrease in amplitude when nitrogen was replaced with N_2O . The decrease was

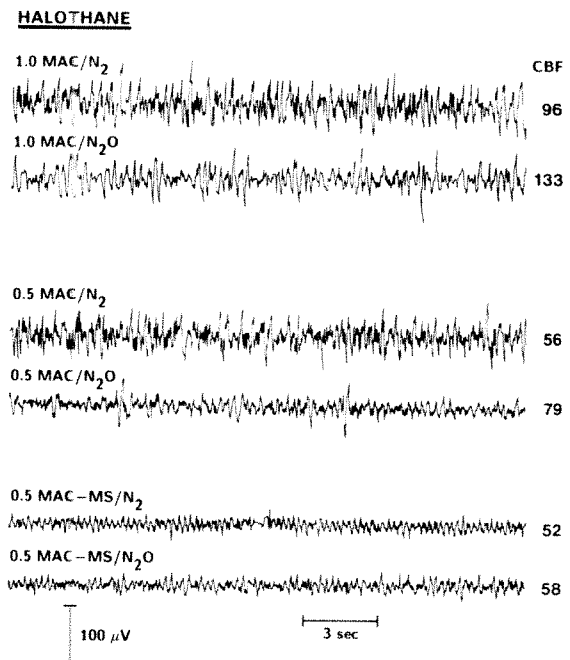


Figure 2. Frontooccipital EEG recorded during the six phases of study (0.5 MAC with and without N_2O , 1.0 MAC with and without N_2O , 0.5 MAC plus morphine with and without N_2O) in a rabbit that received halothane. The six CBF determinations (in $ml \cdot 100 g^{-1} \cdot min^{-1}$) made in this rabbit are presented at the right.

frequently subtle and in two 0.5 MAC/morphine studies it was not observed. A conspicuous difference between the isoflurane and halothane studies was the obvious reduction in overall EEG amplitude produced by morphine in the rabbits given halothane but not in those given isoflurane.

Discussion

Our original thesis was that the increase in CBF reported with the administration of N_2O was, in many instances, the result of administering N_2O to subjects otherwise only marginally anesthetized or completely unanesthetized. We suspected that N_2O might cause an arousal or "second stage" type phenomenon with concomitant increases in cerebral metabolic rate (CMR) and CBF. We surmised that if N_2O were administered with progressively "deeper" levels of anesthesia the associated CBF increases would be attenuated. However, the data we obtained in the present study are inconsistent with this simplistic notion. With both halothane and isoflurane, the increase in CBF associated with N_2O was greater at 1.0 MAC than it was at 0.5 MAC. Furthermore, a large dose of morphine administered to rabbits already receiving 0.5 MAC of either halothane or isoflurane did not significantly alter the effect of nitrous oxide on CBF.

The previously available data regarding the effects of N_2O on CBF appeared to provide reasonable justification for our initial hypothesis. Theye and Michenfelder (1) reported that N_2O increased CMR and CBF when administered to dogs receiving 0.1% halothane but not 0.7% halothane. Sakabe et al. (2) found that N_2O caused a greater increase in CBF in dogs during the administration of 0.2% halothane than during the administration of 0.8% halothane. These authors also reported that administration of thiamylal to dogs receiving 0.2% halothane reduced the increase in CBF caused by N_2O . Manohar and Parks (5) presented data obtained during anesthesia with halothane and N_2O in pigs that are similarly consistent with this pattern. These latter data require interpolation because the halothane and N_2O concentrations were changed simultaneously, but they indicate that the CBF increment in the cerebral hemispheres of pigs caused by 50% N_2O was greater with 0.37% halothane than at 0.72% halothane. Finally, Phirman and Shapiro (8) observed increases in ICP (CBF not measured) in a patient with a closed head injury who was exposed to 70% N_2O twice in rapid succession. The increase did not occur when a third exposure was made after supplementation with diazepam and thiopental.

The general pattern of the foregoing studies clearly suggested that N_2O has a diminishing effect on CBF at deeper levels of anesthesia. However, the present results are not consistent with this pattern. The explanation for the discrepancy is a matter of speculation. The differences may be related to the range of background depths of anesthesia examined. The present study compared 0.5 MAC of a volatile anesthetic with 1.0 MAC and with 0.5 MAC supplemented with a substantial dose of morphine. By contrast, in three of the reports mentioned above, one of the exposures to N_2O was made in very lightly anesthetized (0.1 MAC [1] and 0.2 MAC [2]) or otherwise unanesthetized subjects (8). It is only in the study of Manohar and Parks (5) that an essentially identical range of volatile agent (halothane) concentrations (0.5 and 1.0 MAC) was examined. The pattern of N_2O effect was nonetheless opposite to that which we observed. However, subsequent to the initiation of the present work, these same authors (Manohar and Parks) have presented data concerning the effects of N_2O during anesthesia with isoflurane (6) and enflurane (7). In contrast to their results obtained with halothane (5), the latter data (6,7) indicate that N_2O (50%) causes a greater increase in CBF in the presence of concentrations of anesthetic near 1.0 MAC than near 0.5 MAC. Unequivocally, in our present studies the CBF effects of N_2O were similar during anesthesia with halothane

and isoflurane and these effects paralleled those observed by Manohar and Parks for isoflurane and enflurane (but not halothane). Our review of the three studies by Manohar and Parks, together with the present results, did not reveal any obvious technical/hemodynamic explanation for the discrepancies. However, in the studies by Manohar and Parks, blood flow was determined for the entire cerebral hemisphere (microspheres) whereas in the present study CBF was determined in the parietal cortex using hydrogen clearance. The present CBF values, although inevitably reflecting a contribution from the underlying white matter, are nevertheless restricted regional flow values. Accordingly, the discrepancies between the various studies may be the result of regional heterogeneity in CBF.

In contrast to our observations during anesthesia with increasing concentrations of volatile agents, anesthetic supplementation with a large dose of morphine caused very little change in the effects of N_2O on CBF. The administration of 70% N_2O during anesthesia with 0.5 MAC halothane/morphine (bolus, 10 mg/kg plus infusion, $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$) resulted in an increase in CBF that was not statistically different from that observed with 0.5 MAC halothane alone. With 0.5 MAC isoflurane/morphine, N_2O increased CBF in every rabbit. However, the response was quite variable and the mean increase was not statistically significant. Nonetheless, the effect appears to be little different from that seen with 0.5 MAC isoflurane alone. Morphine itself appears to have had little effect on CBF, as indicated by the very similar CBF values for 0.5 MAC/ N_2 and 0.5 MAC/morphine/ N_2 . There have been no prior studies of the effects of morphine on CBF in rabbits, but our observations are in keeping with the typically modest effects of several narcotics in numerous species (17-19). To our knowledge there have been no previous evaluations of the CBF effects of N_2O when added to a morphine anesthetic with or without simultaneous volatile anesthetic. However, Jobes et al. (20) studied the effects of morphine, 3 mg/kg, plus 70% N_2O in humans and observed that CBF and $CMRO_2$ were unchanged from the unanesthetized control state. This finding might reflect the absence of an effect by either agent but is also consistent with the occurrence of counterbalancing influences. However, the data of Jobes et al. appear consistent with the present observations in that they suggest that large increases in CBF might not be expected as a result of the combination of N_2O with morphine.

The observation that the effect of N_2O on CBF was greater at higher concentrations of halothane and isoflurane than at lower concentrations prompted us to wonder whether the CBF increment that we did ob-

serve with the addition of N₂O to 0.5 MAC/morphine was to a great extent the result of some interaction with the volatile anesthetic. Regrettably, we felt that our model did not permit us to study the effects of N₂O when added to morphine alone. Our experience with the administration of morphine to New Zealand White rabbits indicated that in at least some instances morphine alone does not provide complete anesthesia even in very large doses. Accordingly, we concluded that such an investigation might be inhumane.

In spite of the significant increases in CBF with the administration of N₂O, we did not observe significant increases in ICP. The data do, however, suggest a trend toward increases in ICP and we suspect that our observations reflect the highly compliant intracranial space of normal animals studied in a head-up posture.

We considered the possibility that time (preparation deterioration) might have had some influence on the results, particularly with respect to the morphine studies, which were always performed last. Several observations lead us to believe that this was not a major factor. First, with halothane, CBF during 1.0 MAC/N₂ was always greater than with 0.5 MAC/N₂ regardless of the sequence in which they were measured. This is in keeping with previous observations regarding the effects of halothane on CBF in the rabbit (15,16) and other species (5,21-23). Second, the increase in CBF which occurred at 1.0 MAC was always greater than that at 0.5 MAC, again without respect to the sequence in which the two studies were performed. And third, CBF levels with 0.5 MAC/N₂ and 0.5 MAC/morphine/N₂ (the former always preceded the latter) were essentially identical, suggesting that the progressive decrease in CBF that might be expected in a deteriorating preparation was not occurring.

Our data provide no insight into the mechanism by which an increasing concentration of inhalation anesthetic augments the effect of N₂O on CBF. It might be tempting to surmise that the progressive vasodilation that occurs with an inhalation anesthetic somehow increases the gain of the vasodilating influence of N₂O. This "explanation" might be invoked for halothane, with which CBF values increased between 0.5/N₂ and 1.0 MAC/N₂. However, with isoflurane no comparable vasodilation occurred between 0.5 MAC/N₂ and 1.0 MAC/N₂. As a consequence, CBF was considerably greater with 1.0 MAC/N₂ halothane than with 1.0 MAC/N₂ isoflurane (73 ± 34 and 34 ± 13 ml·100⁻¹·min⁻¹, respectively). However, mean CBF increments attributable to N₂O were essentially identical. Accordingly, the antecedent degree of vasodilation is not the sole determinant of the effect of N₂O.

We cannot exclude the possibility that it is contributory and that other factors are also involved. In support of the existence of other factors is the striking difference in EEG effects observed with halothane and isoflurane at the 1.0 MAC level. The greater degree of apparent EEG activation when N₂O was added to 1.0 MAC isoflurane suggests that a greater degree of metabolic activation may have occurred in this group. Unfortunately, this is a matter of unconfirmed speculation as CMRO₂ was not measured in the present studies.

In summary, our initial speculation was that N₂O-induced increases in CBF are the result of an arousal phenomenon occurring when N₂O is administered to lightly anesthetized or unanesthetized subjects. The results of the present study indicate that this hypothesis is not universally correct. Our results do not exclude the possibility that this phenomenon contributes in some instances, but it cannot be the entire explanation. Our observations further indicate that an increase in the end-tidal concentrations of halothane or isoflurane from 0.5 MAC to 1.0 MAC results in an increase in the CBF increment caused by N₂O in the New Zealand White rabbit. The addition of a large dose of morphine sulphate to 0.5 MAC of either agent had little influence on the effect of N₂O on CBF. The present results, alone and in conjunction with previously available information, indicate that the effects of N₂O on CBF may vary substantially with a changing background anesthetic state. If these data can be extrapolated to humans, they indicate that, intraoperatively, when elevated intracranial pressure or a "tight" cranial surgical field occurs, the possibility that N₂O may in some circumstances be a potent cerebral vasodilator should be considered.

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The Effects of PaCO_2 on the Cerebrovascular Response to Nitrous Oxide in the Halothane-Anesthetized Rabbit

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TODD MM. The influence of PaCO_2 on the cerebrovascular response to nitrous oxide in the halothane-anesthetized rabbit. *Anesth Analg* 1987;66:1090-5.

Several authors have observed that nitrous oxide increases cerebral blood flow (CBF) and/or intracranial pressure (ICP) in experimental situations and in humans. However, the effects of hypocapnia on the cerebrovascular responses to N_2O have not been investigated. Therefore, six New Zealand White rabbits were anesthetized with ≈ 1.0 MAC halothane (mean end-tidal concentration 1.26%) and surgically prepared for recording of ICP, the EEG, and both cortical and global CBF (by the H_2 -clearance method). After preparation was complete, measurements were obtained during ventilation with 70% nitrogen (in O_2), and after the inspired gas mixture was changed to 70% N_2O (still with 1.0 MAC halothane). Two such data pairs (N_2 - N_2O) were obtained, one during hypocarbia ($\text{PaCO}_2 \approx 20$ mm Hg) and the other during normocarbia ($\text{PaCO}_2 \approx 40$ mm Hg) conditions. Mean

arterial pressure (MABP) was held constant within each data pair by infusing angiotensin II as needed.

Nitrous oxide resulted in a consistent increase in EEG frequency and decrease in amplitude as compared with N_2 , and produced small (≈ 1 mm Hg) but statistically significant increases in ICP during both hypo- and normocarbic conditions. Nitrous oxide administration also increased CBF as measured both in frontal cortex and globally, with similar changes seen during hypo- and normocarbic conditions, e.g., cortical CBF increased from 42 ± 8 to 59 ± 15 $\text{ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ during hypocarbia, and from 61 ± 13 to 75 ± 15 $\text{ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ during normocarbia. These results confirm that N_2O is a potent cerebrovasodilator in the rabbit, and also indicate that reductions in PaCO_2 do not blunt the cerebrovascular responses to N_2O .

Key Words: ANESTHESIA—neurosurgical. ANESTHETICS, VOLATILE—halothane. ANESTHETICS, GASEOUS—nitrous oxide. BRAIN—blood flow, electroencephalography, intracranial pressure.

Nitrous oxide has been a part of neuroanesthetic practice for decades. Nevertheless, many authors have shown that N_2O can increase cerebral blood flow (CBF) and intracranial pressure (ICP) in animals and in humans (1-10). This appears to be particularly true when the gas is added to a volatile anesthetic, or when used alone. However, many questions remain concerning the effects of N_2O (11,12). One of these involves the influence of PaCO_2 . Recently, Scheller et al. noted that PaCO_2 significantly altered the CBF responses to halothane and isoflurane (13), while Drummond and Todd noted that the CBF- PaCO_2 response curves were different with different anesthetics (14). Furthermore, the effects of PaCO_2 on the ICP changes produced by these volatile agents are well known (15,16). However, no information exists concerning the influence of PaCO_2 on the cerebrovascular responses to N_2O .

Because hypocapnia is an almost universal component of neurosurgical anesthetics that employ N_2O , we chose to examine the changes in CBF, ICP, and the electroencephalogram produced by the administration of N_2O to both hypocarbic and normocarbic, halothane-anesthetized rabbits.

Materials and Methods

Preparation

All experiments were approved by the Animal Care Committee of the University of Iowa School of Medicine. Six New Zealand White rabbits of either sex, weighing 3.4 ± 0.3 kg (mean $\pm$ SD) were anesthetized with 4% halothane/ O_2 in a closed plexiglas box. A 22-gauge catheter was inserted into a marginal ear vein, and the trachea intubated with a 3.0-mm inner diameter cuffed tube, after which 1 mg of pancuronium bromide was given IV, and mechanical ventilation begun with a tidal volume of ≈ 15 ml/kg, at a rate of ≈ 35 breaths/min using an inspired gas mixture of 1% halothane in 70% nitrogen/ O_2 . Carbon dioxide was

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added to the inspired gas mixture to maintain normocarbica as initially assessed by expired gas analysis, and later by measurement of arterial blood gas tensions. A thermistor was passed into the esophagus and the rabbit's temperature thereafter maintained at 38°C using a servocontrolled warming pad. A maintenance IV infusion of lactated Ringer's solution was started at a rate of 4 ml·kg⁻¹·hr⁻¹. Pancuronium was added to this fluid in amounts sufficient to ensure the delivery of ≈0.75–1.0 mg of drug per hour.

The rabbit was then turned supine, and 0.25% bupivacaine was infiltrated into the left or right groin. A cutdown was performed and PE-90 catheters were inserted via the femoral vessels into the abdominal aorta and the right atrium. The atrial catheter was positioned by examination of the transduced pressure waveform (usually during pullback from the right ventricle). The catheters were secured, and the rabbit was turned into the prone position and the head fixed into a stereotactic frame (David Kopf Instruments) with the interaural line located 11–12 cm above the midthorax. The scalp was infiltrated with 0.25% bupivacaine, and a midline incision was made. The scalp was reflected bilaterally, exposing the calvarium, and the bregma (the crossing of the sagittal and coronal sutures) was marked. Small (1–1.5 mm diameter) burr holes were then drilled in the following locations: 1) 5 mm anterior to the bregma and 5 mm to the left of the midline ("left frontal"); 2) 5 mm anterior and 5 mm to the right of the midline ("right frontal"); and 3) 9 mm posterior and 8 mm to the right of the midline ("right parietal"). Finally, a 2–3-mm diameter hole was drilled at the level of the occipital protuberance to expose the confluence of cerebral venous sinuses. An 18-gauge Tuohy needle was stereotactically inserted into the right lateral ventricle via the "right parietal" burr hole (exact coordinates 9 mm posterior, 8 mm lateral, 6–7 mm deep as measured from the point of dural contact), and 250-μm diameter platinum needle electrodes (Grass Instruments E2 subdermal electrodes) were placed into the exposed venous confluence and into left and right frontal cortex. The venous needle was inserted in such a way that ≈1 mm of the needle tip lay within the vessel lumen, while the frontal electrodes were inserted a distance of 2.5 mm beyond the point of dural contact (which leaves the electrode tip near the junction of grey and white matter). These electrodes were used for the determination of CBF, using the H₂-clearance method (17). All holes were then sealed with Permabond 910 cyanoacrylate cement. Two additional needle electrodes were placed into the scalp to permit the recording of a single channel, biparietal EEG, and finally, an Ag-AgCl₂ ECG electrode was placed on a

shaved area of skin on the rabbit's back to serve as a reference electrode for CBF determinations. No external polarizing voltage was used.

Continuously displayed variables in all rabbits included esophageal temperature, FI_{O₂}, expired CO₂, and halothane concentrations, EEG, and arterial, right atrial, and intracranial pressures (all pressures expressed as electrical means at end-expiration) (abbreviated MABP, RAP, and ICP, respectively) with MABP and ICP referenced at head level to permit accurate calculation of cerebral perfusion pressure (CPP = MABP – ICP)]. Heart rate (HR) was calculated manually from the arterial pressure recording. Arterial blood samples (1-ml volumes) were intermittently sampled for the determination of blood gas tensions and pH. Cerebral blood flow was simultaneously measured from each of the three platinum electrodes. Hydrogen (≈3–5%) was added to the inspired gas mixture until a stable electrode current was achieved. Hydrogen was then abruptly discontinued and CBF calculated by the T_{1/2} method (18), after discarding the initial 30 sec of the washout curve. This 30-sec wait is the time needed to permit arterial [H₂] to fall by >95% (as determined in this laboratory), hence minimizing confusion produced by arterial recirculation. At each data point, CBF values from the two frontal electrodes were averaged and are reported as "CBF-frontal cortex," whereas the values from the venous confluence (which drains most of the forebrain) are denoted "CBF-forebrain."

After surgical preparation was complete, and the correct performance of the H₂ electrodes was confirmed, end-tidal halothane concentration was adjusted to values of ≈1 MAC (=1.39%) (19). These concentrations were maintained for a minimum of 30 min before the first measurements were recorded.

Experimental Protocol

All experiments consisted of two pairs of measurements. In each pair, data were first collected during ventilation with 70% N₂ in oxygen, and then during the administration of 70% N₂O (the reverse order, e.g., N₂O–N₂ was not studied). One data pair was obtained under normocarbic conditions (PaCO₂ ≈ 40 mm Hg), whereas the second pair was obtained during hypocarbica (PaCO₂ ≈ 20 mm Hg). To minimize any effects of order, the first pair of recorded data was obtained during hypocarbica (followed later by normocarbic conditions) in half of the rabbits, whereas in the remainder, the first measurements were conducted during normocarbica. To simplify description, only the detailed protocol for the "normocarbic-hypocarbica" sequence will be described.

Table 1. Data Summary

	Hypocapnia			Normocapnia			Hypocapnia vs normocapnia
	N ₂	N ₂ O	P value ^a	N ₂	N ₂ O	P value ^a	P value ^b
ET _{halo} (%)	1.23 ± 0.03	1.25 ± 0.04	—	1.27 ± 0.04	1.27 ± 0.04	—	—
PaO ₂ (mm Hg)	176 ± 27	175 ± 19	—	176 ± 23	171 ± 24	—	—
PaCO ₂ (mm Hg)	22 ± 3	21 ± 2	—	40 ± 3	40 ± 4	—	—
pH (units)	7.55 ± 0.06	7.53 ± 0.04	—	7.37 ± 0.03	7.37 ± 0.04	—	—
HR (beats/min)	277 ± 23	286 ± 22	NS	271 ± 33	286 ± 17	NS	NS
MABP (mm Hg)	74 ± 9	77 ± 10	NS	74 ± 7	75 ± 10	NS	NS
CVP (mm Hg)	2.8 ± 1.2	2.9 ± 1.7	NS	2.3 ± 0.7	2.5 ± 0.8	NS	NS
ICP (mm Hg)	5.0 ± 1.4	6.3 ± 2.0	0.04	6.3 ± 2.0	7.0 ± 2.6	0.03	NS
CPP (mm Hg)	69 ± 9	71 ± 9	NS	68 ± 8	68 ± 11	NS	NS
Angiotensin (ng·kg ⁻¹ ·min ⁻¹)	22 ± 8	15 ± 17	NS	21 ± 21	26 ± 26	NS	NS
CBF (ml·100 gm ⁻¹ ·min ⁻¹)							
Frontal cortex	42 ± 8	59 ± 15	0.03	62 ± 13	75 ± 15	0.03	NS
Forebrain	47 ± 7	76 ± 15	0.01	67 ± 14	78 ± 8	0.04	0.05

All values are mean ± SD, n = 6.

Abbreviations: ET_{halo}, end-tidal halothane concentrations; HR, heart rate; MABP, mean arterial blood pressure; CVP, central venous pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; CBF, cerebral blood flow.

^aP values are obtained by paired testing of N₂ vs N₂O values at each PaCO₂ level.

^bP values are for comparisons of changes produced by N₂O in hypocarbic vs normocarbic states (unpaired t-test).

Thirty minutes after completion of the surgical procedure, an arterial blood sample was drawn to verify normocarbica. Hydrogen administration was then begun, and 7–9 min later, hemodynamic variables were recorded (HR, MABP, RAP, ICP) along with the EEG, an arterial blood sample was obtained, and H₂ was discontinued. The actual recording of the H₂ clearance curve required ≈10 additional minutes. When completed, N₂ was replaced with 70% N₂O, H₂ gas was again administered and, after ≈20 min of N₂O inhalation, the above sequence of measurements was repeated. When completed, N₂O was discontinued, and replaced with N₂. Carbon dioxide concentration in the inspired gas mixture was then reduced over ≈10 min (to an end-tidal CO₂ ≈ 15–20 mm Hg). This concentration was held constant for another 15–20 min (after verification of the desired degree of hypocapnia by blood gas determination), and the paired sequence of recordings during N₂ and N₂O administration were then repeated.

Because arterial blood pressure may be a determinant of CBF during halothane anesthesia (20), an effort was made during the experiment to ensure that 1) a minimum MABP of 65 mm Hg was maintained at all times, and 2) that MABP during both components of the N₂–N₂O pair was similar. When necessary, this was accomplished by the IV infusion of a dilute solution of angiotensin II (human form; synthetic, Sigma Chemical). Angiotensin II was chosen over other agents because of its less potent direct cerebral vasoconstrictive effects (21).

Statistical Analysis

The effects of nitrous oxide were based on two measurements obtained <30 min apart in the same animal and so were evaluated—at each PaCO₂ value—by a paired *t*-test. However, all other comparisons, e.g., comparison of the responses to N₂O at the two PaCO₂ levels, were made using an unpaired *t*-test. A *P* value of < 0.05 was accepted as statistically significant.

Results

All data are presented in Table 1. As intended, there were no significant changes or differences in expired halothane concentration or PaO₂ during the study, and PaCO₂ and pH values changed only as intended (no N₂O effects). Note, however, that in spite of the experimental plan, actual end-tidal halothane values were only ≈0.9 MAC.

Under both hypocarbic and normocarbic conditions, visual inspection of the EEGs indicated that N₂O administration resulted in a consistent increase in dominant EEG frequency and an often marked decrease in maximal amplitude (See Fig. 1). The onset of these EEG changes was rapid (<3 min), with stable patterns present within <10 min regardless of PaCO₂. There were no consistent differences in EEGs between normo- and hypocarbic-nitrogen tracings, although recordings made during hypocapnia tended to be dominated by high-amplitude slow waves.

Neither N₂O nor PaCO₂ had any significant effect

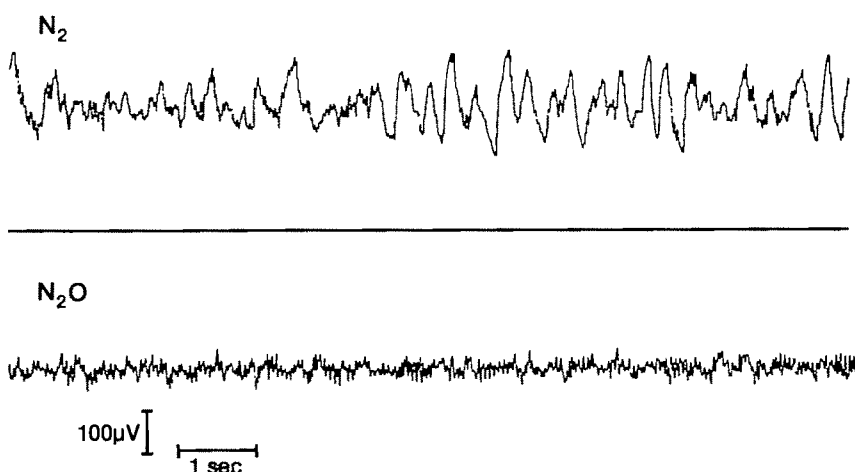


Figure 1. Biparietal EEGs recorded in a hypocapnic rabbit during ventilation with N₂ (top trace) and 70% N₂O (bottom trace). Note the increase in frequency and decrease in maximal amplitude with the addition of N₂O.

on HR, MABP, or CVP. There were also no differences in doses of angiotensin II used at any point (range 15–26 ng·kg⁻¹·min⁻¹). N₂O administration did produce small (<1 mm Hg) but statistically significant increases in ICP during both hypo- and normocapnia, but with no significant changes or CO₂-related differences in CPP.

Both cortical and forebrain CBF values during hypocarbic ventilation with N₂ were significantly lower than those noted during normocarbica, demonstrating the preservation of PaCO₂-responsiveness in this preparation. Nitrous oxide administration produced significant increases in both cortical and forebrain CBF during both hypo- and normocarbica. There were no CO₂-related differences in the magnitude of the changes recorded from the cortical electrodes (i.e., a 17-ml·100 g⁻¹·min⁻¹ increase during hypocarbica vs a 14-ml·100gm⁻¹·min⁻¹ increase during normocapnia). However, the increase in forebrain CBF produced by N₂O was greater during hypocapnia (29 ml·100gm⁻¹·min⁻¹) than during normocapnia (11 ml·100g⁻¹·min⁻¹) although the statistical difference in these values only just exceeded a *P* value of 0.05.

Discussion

Most available information indicates that clinically relevant concentrations of nitrous oxide are capable of producing significant increases in CBF and ICP in animals and humans. For example, Laitinen et al. (1) and Henriksen and Jorgensen (3) noted that N₂O (when given to otherwise unanesthetized, spontaneously breathing neurosurgical patients) produced consistent and often dramatic increases in ICP. Laitinen et al. also showed an increase in pulsatile cerebral impedance (regarded as an indirect measure of CBF although it may be more of a reflection of cerebral

blood volume). More recently, Fitzpatrick et al. reported that N₂O decreased cerebrovascular resistance in a normocarbic isolated canine brain preparation (9), and Pelligrino et al. observed an ≈60% increase in CBF in spontaneously breathing goats (10). Similar findings have been made when N₂O is added to an established halothane anesthetic. Sakabe et al. noted that in normocarbic dogs anesthetized with ≈1 MAC halothane, the substitution of 60% nitrous oxide (for nitrogen) resulted in a rapid increase in global CBF (measured by the venous outflow method), from ≈65 ml·100gm⁻¹·min⁻¹ to a maximum of 107 ml·100gm⁻¹·min⁻¹ (a 64% increase) (7). These same authors noted a roughly similar increase in "CBF equivalent" produced by N₂O in halothane-anesthetized humans (5). In both studies, the maximal response had occurred within 15 min of the start of N₂O administration and was maintained at stable levels thereafter (for up to 1 hr).

In general, the results obtained in the current study confirm those noted above, with 70% N₂O causing a significant (although clinically unimportant) increase in ICP, and a 20–40% increase in CBF. This change in CBF is somewhat less than reported by others (although it is almost as large as the CBF changes produced by a 20 mm Hg increase in PaCO₂). However, the concentration of N₂O used in this study may be comparatively low. There are no published values for N₂O MAC in the rabbit, and only two values for halothane MAC: 0.82 (22) and 1.39% (19). We chose to use the latter value, because we were more familiar with the circumstances surrounding its derivation. If one uses the ratio test described by Drummond (19), who notes that the ratio of MAC values for any two volatile agents is approximately constant across species, one can estimate an N₂O MAC value between 149 and 182%. This is based on the rat N₂O/halothane

MAC ratio of $135/1.14 = 119$ and a rabbit halothane MAC value of 1.39, and is modified by assuming a 10% coefficient of variation for such ratio calculations (19). The current study would thus have been carried out using a roughly 0.4–0.5 MAC, compared with 0.6 MAC levels used in several of the previously mentioned studies. This calculation obviously assumes that the ratio approach noted can be extrapolated to N_2O , and that the value for halothane MAC we used is accurate. Nevertheless, it also suggests that the concentrations of N_2O used are within the clinically relevant range.

An extensive literature search failed to locate any information concerning the role played by $PaCO_2$ in determining the CBF responses to N_2O . Misfeldt et al. (4) noted that N_2O increased ICP by only ≈ 3 mm Hg in ventilated patients with $PaCO_2$ levels of ≈ 25 mm Hg, an increase less than that reported by others during normocapnia (3). Conversely, both Phirman and Shapiro (6) and Moss and McDowall (8) observed clinically important ICP increases in hypocarbic patients given N_2O . Unfortunately, changes in intracranial compliance with changing $PaCO_2$ make it difficult to interpret ICP alterations in terms of CBF. However, the current study indicates that hypocapnia clearly does not attenuate the CBF response to N_2O . In fact, a comparison of the responses seen during hypo- and normocapnia suggests that the increase in CBF produced by N_2O during hypocarbia may be greater than that seen during normocarbia, although the statistical support for this conclusion is weak. This observation contrasts with those obtained for volatile anesthetics. For example, examination of the data of Scheller et al. (13) suggests that hypocapnia acts to alter the CBF response to both halothane and isoflurane (at least when given in the presence of a morphine-nitrous oxide background), and a similar observation has been noted in humans anesthetized with halothane, both in terms of CBF (23) and ICP (15). This lack of hypocapnic attenuation with N_2O also differs from that seen with other vasodilators, including CO_2 itself. The CBF- $PaCO_2$ response curve is curvilinear with a gradually increasing slope (as $PaCO_2$ increases) (14; also Todd, unpublished observations in the rabbit). This indicates that an incremental increase in $PaCO_2$ yields a smaller increase in CBF if applied during hypocapnia rather than during normo- or hypercapnia.

The reasons for the lack of hypocarbic attenuation of N_2O -induced vasodilation remain unknown. They may be related to the underlying mechanism by which N_2O produces its effects. Nitrous oxide (or any anesthetic) may increase CBF by one or by a combination of as many as three (or more) mechanisms: 1) a direct

relaxant effect on vascular smooth muscle (such as that produced by sodium nitroprusside); 2) an increase in cerebral metabolic activity with a resultant coupled increase in CBF; and/or 3) a direct effect on vasomotor control centers with resultant neurally mediated changes in flow. The first of these possibilities seems to be the least likely explanation for the observed CO_2 - N_2O interaction, because such an effect would most likely be blunted by an opposing vasoconstriction due to hypocarbia. Metabolic increases caused by N_2O have been described by some workers (7,10), but not by others (24). Several groups have also demonstrated that the administration of "metabolic depressant" drugs such as narcotics or barbiturates blunts the CBF/ICP response to N_2O (Phirman and Shapiro [6] and Drummond et al., [25]). However, because metabolic rates were not measured in the current study, further comment is unwarranted. The final, and perhaps the most likely possibility relates to electrical activation. During both hypo- and normocapnic conditions, N_2O administration resulted in an "activation" of the EEG (decreased amplitude, increased frequency). This differs from the change seen with volatile agents. The EEG during hypocapnia/ N_2 appeared to be somewhat "slower" than during normocarbia, and hence the change produced by N_2O was more pronounced (see Fig. 1). Furthermore, hypocapnia alone is commonly used to "activate" the EEG during diagnostic testing, and it is possible that such conditions may be synergistic with any N_2O effects. This exaggerated response during hypocarbia may have acted to offset any vasoconstricting effects of $PaCO_2$. Such EEG activation may influence CBF in two ways, either through increases in metabolism (see above), or it may be associated with increased activity in neural pathways that directly influence vessel diameter (via vasomotor control centers).

We do not believe that our findings are somehow "artificially" related to differing rates of N_2O washin produced by the different levels of $PaCO_2$. Hypocapnia decreases CBF and slows cerebral equilibration with N_2O . If the response to N_2O were biphasic, with a rapid increase and subsequent decrease in CBF, it might have been possible that we caught the "peak" CBF during hypocapnia, but missed it during normocapnia. However, available information indicates that the response to N_2O is maximal within <10 min after the start of inhalation and remains unchanged for the next hour (5,7,10). Therefore, the 20 min we provided for N_2O equilibration should have been adequate. Furthermore, even during hypocapnia, baseline (nitrogen) CBF values were not dramatically depressed (presumably because of halothane vasodilation), and the EEG changes produced by N_2O had

been stable for 5–10 min before flow measurements were recorded (regardless of PaCO₂).

Given the speculative nature of the above discussion, we must caution against extrapolation of the present findings to clinical practice. The work was carried out in rabbits and employed halothane as the background anesthetic (which is currently unusual in neuroanesthesia). We do not know whether different anesthetics (e.g., isoflurane, narcotics, etc.) might alter the observed responses, although Drummond et al. have noted that CBF increases after the administration of N₂O to isoflurane-anesthetized rabbits (25). We also do not know how these changes in CBF will translate into increases in ICP in the diseased brain. In such circumstances, the ICP response is dependent on intracranial compliance (which explains the small increases in ICP in our rabbits with normal compliance). Hence, although hypocapnia may not alter the CBF responses, it may substantially alter the changes in ICP. Furthermore, the clinical consequences of such changes in CBF are entirely unknown, and it should be remembered that N₂O has been successfully used during neuroanesthesia for decades. Therefore, at present this report serves only to reinforce the recognition that N₂O, at least under some circumstances, is a potent cerebral vasodilator and that this effect is not prevented by hypocapnia. Translation of this recognition into changes in practice must await further substantial experimental work.

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Cardiovascular Responses to Acute Loading with Nifedipine Alone and Nifedipine plus Propranolol during Inhalation Anesthesia in Monkeys

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DEWOLF AM, MARQUEZ JM, NEMOTO EM, KANG YG, PINSKY MR. Cardiovascular responses to acute loading with nifedipine alone and nifedipine plus propranolol during inhalation anesthesia in monkeys. *Anesth Analg* 1987;66:1096-103.

The cardiovascular effects of the administration of nifedipine and nifedipine combined with propranolol were examined in 15 monkeys during 0.75 and 1.25 MAC of anesthesia with isoflurane, enflurane, or halothane. Hemodynamic variables measured included heart rate (HR), mean arterial pressure (MAP), left ventricular end-diastolic pressure (LVEDP), maximum rate of increase of the left ventricular pressure (max LV dP/dt), and thermodilution cardiac output (CO). The infusion of nifedipine at a rate adequate to produce therapeutic blood levels during 0.75 MAC with each anesthetic decreased MAP and SVR, but had no effect on cardiac index (CI), max LV dP/dt, or HR. Increasing the anesthetic concentration from 0.75 to 1.25 MAC during nifedipine administration decreased HR and MAP in all groups and decreased CI with halothane and enflurane, but

not with isoflurane. Addition of propranolol by infusion in amounts adequate to produce 75% β -adrenergic blockade caused a further depression of CI, max LV dP/dt, HR, and MAP. However, the hemodynamic depression was significantly greater with halothane and enflurane than with isoflurane. Intravenous administration of calcium chloride (10 mg/kg) after calcium channel and β -adrenergic blockade only partially reversed the hemodynamic depression that occurred with all three anesthetics. It was concluded that acute loading with nifedipine with and without propranolol exerts a greater cardiovascular depressant effect during enflurane or halothane anesthesia than during isoflurane anesthesia. The myocardial depressant effects of nifedipine and propranolol may be synergistic with the depressant effects of potent inhalation anesthetics.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane. HEART—myocardial function. IONS—CALCIUM CHANNEL BLOCKERS, calcium chloride. PHARMACOLOGY—nifedipine, propranolol.

Patients with coronary artery disease are often treated with a combination of β -adrenergic and calcium channel-blocking agents (1) because their effects on myocardial oxygen supply-demand ratio are complementary (2,3).

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The hemodynamic interactions of some calcium blocking agents with potent inhalation anesthetics have been previously described. Acute loading with verapamil is tolerated better hemodynamically during isoflurane anesthesia than during either halothane or enflurane anesthesia (4-8). The hemodynamic effects during anesthesia of another calcium channel blocker, nifedipine, have been studied (9-12). Acute loading with nifedipine produced hypotension secondary to systemic vasodilation while maintaining cardiac output by initiating a reflex sympathetic activation. β -Blockade during anesthesia in the presence of nifedipine may suppress this reflex increase in sympathetic activity, resulting in an additional hypotensive effect. The cardiovascular effects of acute loading with nifedipine and nifedipine combined with propranolol have not been described during anesthesia with the three commonly used inhalation agents. Our aim was to compare the relative cardiovascular depressant ef-

fects of isoflurane, enflurane, and halothane during administration of nifedipine alone and nifedipine combined with propranolol.

Methods

With the approval of the institutional animal care committee, adult Cynomolgous monkeys ($n = 15$) weighing 5.1–9.4 kg (mean, 6.3) were randomly assigned to one of three equal groups and anesthetized with either isoflurane, enflurane, or halothane. The MAC levels reported for adult humans (isoflurane, 1.2%; enflurane, 1.68%; halothane, 0.8%) were used. Anesthesia was induced by insufflation of high concentrations of the inhalation anesthetic in 66% N₂O and 33% O₂. After paralysis with intravenous pancuronium (0.1 mg/kg), and tracheal intubation, the monkeys were ventilated (Harvard ventilator) with a nonrebreathing system using tidal volumes of 15 ml/kg, 5 cm H₂O of PEEP, and a respiratory rate adjusted to maintain endtidal CO₂ at $5 \pm 0.5\%$. During instrumentation anesthesia was maintained with 1 MAC of the inhalation anesthetic in 100% O₂. Vaporizer accuracy was checked daily with a calibrated anesthetic gas analyzer (Engstrom Emma, Bromma, Sweden). Throughout the studies 0.9% NaCl with 5% dextrose was infused at a rate of $4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. Rectal temperature was continuously monitored and maintained at $37.5 \pm 0.5^\circ\text{C}$ by external heating.

A 5-French, thermodilution flow-directed pulmonary arterial catheter and a femoral arterial catheter were inserted for pressure monitoring and sampling of arterial blood. Cardiac output was measured in triplicate by thermodilution using 5 ml 4°C 0.9% NaCl. A 5-French, micromanometer-tipped catheter (Millar Instruments, Inc., model PC 350) was externally calibrated and then introduced into the left ventricle via the left carotid artery to monitor the left ventricular end-diastolic pressure after the "a" wave (LVEDP) and the maximal rate of rise of the left ventricular pressure (max LV dP/dt), which was obtained electronically. All pressures were measured at end-expiration. Lead II of the electrocardiogram (ECG) was also continuously recorded for determination of heart rate (HR) averaged over 10 sec. The LVEDP was kept at $10 \pm 2 \text{ mm Hg}$ throughout the study by administration of hydroxyethyl starch or by blood withdrawal, as necessary. Twenty minutes was allowed before hemodynamic measurements were made. After insertion of the catheters, reconcentration of anesthetic in inspired air was set at 0.75 MAC for 30 min before determination of baseline values. This resulted in a stable hemodynamic state in all monkeys.

The following variables were measured at selected times, as described later: arterial blood pressure, pulmonary artery pressure, LVEDP, max LV dP/dt, cardiac output (CO), arterial gas tensions, and hematocrit (Hct). Mean arterial pressure (MAP) was calculated as the diastolic arterial pressure plus one-third the pulse pressure. From these measurements the following derived variables were calculated using standard formulas: cardiac index (CI), stroke volume (SV), stroke index (SI), left ventricular stroke work (LVS_W), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR). Arterial plasma samples were also collected for determination of plasma propranolol levels using HPLC-UV detection (Waters) by the method of Nation et al. (13).

Nifedipine solution for intravenous infusion was prepared by adding 10 mg nifedipine to 5 ml ethyl alcohol, 25 ml ethylene glycol, and 20 ml normal saline solution, for a final concentration of 200 $\mu\text{g}/\text{ml}$. The solution was shielded from light. After baseline measurements at 0.75 MAC, nifedipine was infused at a rate of $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 11 min and continued at $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ thereafter (14,15) to achieve a plasma level of about 70 ng/ml, which decreases MAP by about 10% and which is in the therapeutic range (16). After 30 min of equilibration, measurements were made at 0.75 MAC. To determine the hemodynamic effects of increasing the level of anesthesia during nifedipine administration, anesthesia was increased to 1.25 MAC, and the measurements were repeated 20 min later.

While the nifedipine infusion was maintained, propranolol infusion was begun and the anesthetic level decreased to 0.75 MAC. Propranolol was also administered at two consecutive continuous infusion rates of $7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 20 min, followed by $0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to obtain a calculated plasma level of about 35 ng/ml, which produces about 75% β -adrenergic blockade in humans (17). In preliminary studies in Cynomolgous monkeys, this plasma level also caused a significant depression in the dose-response of HR to isoproterenol (1 mg IV). Measurements were again made at 0.75 and 1.25 MAC of the anesthetic in 100% O₂. Finally, at 1.25 MAC with continued infusion of nifedipine and propranolol, 10 mg/kg CaCl₂ was given IV as a bolus, and all measurements were repeated 3 min later.

Six additional monkeys were randomly anesthetized with isoflurane, enflurane, or halothane ($n = 2$, each subgroup), and hemodynamic variables were measured as described earlier. Anesthetic concentrations were set as described earlier, but neither nifedipine nor propranolol was administered. These monkeys served as controls to determine hemodynamic changes over time with anesthetic alone.

The data were analyzed by analysis of variance (ANOVA) for repeated measures. Statistical significance of within- and between-group differences were compared by the Student-Newman-Keuls test. Statistical significance was assumed with a $P < 0.05$. All data are presented as mean $\pm$ SE.

Results

Data on CI, MAP, HR, and SVR in the control group are presented in Figure 1 as the mean of two measurements. These data were not analyzed statistically because of the small number of animals in each group. Although each anesthetic affected the various hemodynamic variables, there was no apparent temporal hemodynamic response independent of MAC level for each anesthetic agent.

In the study group, arterial blood gas tensions remained stable throughout the experiment. Only after CaCl_2 administration in the enflurane and halothane groups did pH_a decrease significantly below baseline. Plasma propranolol levels (Table 2) were similar in the three anesthetic groups (range 19.4–35.0 ng/ml); in a subgroup of two monkeys with the same propranolol levels, HR did not increase in response to a test dose of isoproterenol (1 mg IV).

Hemodynamic responses in the three anesthetic groups are summarized in Table 1 and Figure 2. In Figure 2, results during the protocol are compared with the previous step, whereas in Table 1, the results are compared with baseline values. By experimental design, LVEDP remained constant at 10 mm Hg throughout the study. In all groups there was a progressive but equal decrease in hematocrit. During baseline anesthetic conditions (0.75 MAC), MAP was highest with isoflurane, and CI was lowest with halothane. Heart rate, max LV dP/dt, SVR, and PVR were similar in all groups.

At 0.75 MAC anesthesia, nifedipine infusion was associated with a significant decrease in MAP only during isoflurane. This decrease in MAP was associated with a small but statistically nonsignificant decrease in SVR. In all anesthetic groups, CI, max LV dP/dt, and HR remained unchanged. Increasing the depth of anesthesia to 1.25 MAC decreased MAP in all groups and decreased HR and CI during enflurane and halothane anesthesia. Absolute levels of MAP and CI were highest with isoflurane.

At each anesthetic level, the addition of propranolol to nifedipine was compared with nifedipine administration alone. Propranolol infusion during nifedipine administration was associated with a decrease in HR, MAP, CI, and max LV dP/dt in all groups at both levels of anesthesia. Systemic vascular resist-

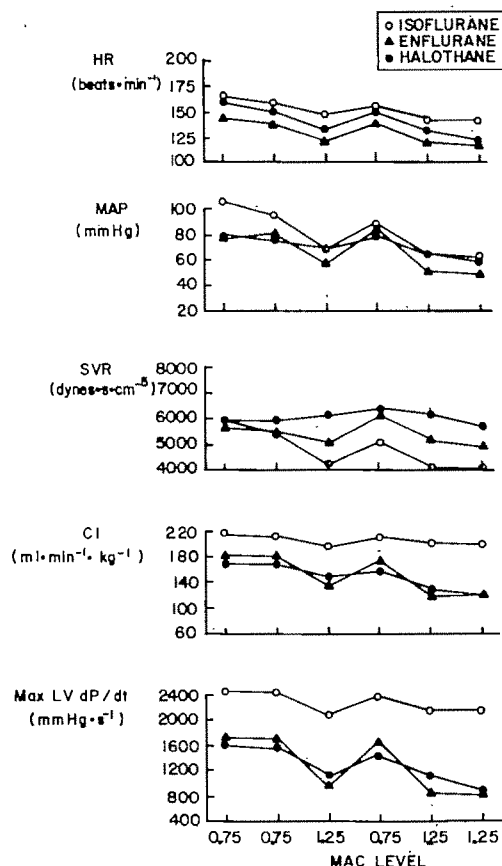


Figure 1. Hemodynamic effects of changing anesthetic concentration without drug administration in the control groups. Open circles, isoflurane; filled triangles, enflurane; filled circles, halothane. Mean values are shown. $n = 2$ for each anesthetic.

ance increased only during 0.75 MAC with isoflurane and enflurane. The predominant hemodynamic effect of propranolol was a reduction in HR and CI. Increased depth of anesthesia during nifedipine and propranolol administration (Fig. 2) was associated with decreases in MAP and CI. Maximum rate of increase of the left ventricular pressure decreased more with halothane and enflurane than with isoflurane. Decreases in CI at equal MAC levels of anesthesia during infusion of nifedipine alone and during infusion of both nifedipine and propranolol were as follows for each anesthetic agent at 0.75 MAC and 1.25 MAC, respectively: isoflurane, 36% and 35%; enflurane, 41% and 37%; and halothane, 39% and 30%. Relative to each other, isoflurane was associated with the highest absolute levels of MAP and CI in the presence of nifedipine alone or with nifedipine in combination with propranolol. At an anesthetic depth of 1.25 MAC, nifedipine alone was tolerated better during isoflurane anesthesia than during enflurane or halothane anesthesia. Similarly, 1.25 MAC of isoflurane in the presence of nifedipine and propranolol was associated with an MAP 30% above the MAP observed dur-

Table 1. Hemodynamic Variables in Monkeys during Isoflurane, Enflurane, and Halothane Anesthesia with Infusion of Nifedipine and Propranolol, and Bolus Injection of Calcium Chloride

		Drug given (MAC)					
		— (0.75)	N (0.75)	N (1.25)	N + P (0.75)	N + P (1.25)	N + P + Ca (1.25)
HR (beats/min)	I	168 ± 8	179 ± 8	162 ± 6	140 ± 10 ^a	132 ± 9 ^a	132 ± 11 ^a
	E	179 ± 7	187 ± 4	167 ± 4 ^a	136 ± 5 ^a	130 ± 4 ^a	132 ± 3 ^a
	H	169 ± 11	170 ± 11	144 ± 12 ^a	124 ± 7 ^a	113 ± 10 ^a	118 ± 7 ^a
MAP (mm Hg)	I	106 ± 3 ^{b,c}	95 ± 5 ^{a,b,c}	72 ± 4 ^{a,b,c}	86 ± 4 ^{a,b,c}	61 ± 4 ^{a,b,c}	65 ± 6 ^{a,b,c}
	E	79 ± 5 ^b	71 ± 4 ^b	53 ± 3 ^{a,b}	63 ± 8 ^{a,b}	44 ± 4 ^{a,b}	52 ± 5 ^{a,b}
	H	80 ± 6 ^c	72 ± 4 ^c	49 ± 7 ^{a,c}	55 ± 7 ^{a,c}	38 ± 5 ^{a,c}	48 ± 5 ^{a,c}
LVEDP (mm Hg)	I	11.8 ± 1.0	9.8 ± 0.9	11.0 ± 0.9	11.6 ± 0.5	12.2 ± 0.9	11.8 ± 0.6
	E	11.8 ± 0.7	9.8 ± 0.5	9.8 ± 0.7	12.0 ± 1.1	11.4 ± 0.8	11.0 ± 0.9
	H	9.4 ± 0.8	9.8 ± 0.4	10.2 ± 0.7	11.2 ± 0.6	11.0 ± 0.5	10.8 ± 0.7
Max LVdP/dt (mm Hg/sec)	I	1680 ± 159	1670 ± 136	1420 ± 107 ^c	1200 ± 138 ^{a,b,c}	1030 ± 136 ^{a,b,c}	1180 ± 183 ^{a,b,c}
	E	1440 ± 68	1460 ± 68	1190 ± 108 ^d	910 ± 84 ^{a,b}	690 ± 66 ^{a,b}	860 ± 68 ^{a,b}
	H	1500 ± 263	1420 ± 206	780 ± 183 ^{a,c,d}	760 ± 121 ^{a,c}	480 ± 146 ^{a,c}	700 ± 119 ^{a,c}
CI (ml·min ⁻¹ ·kg ⁻¹)	I	191 ± 12 ^c	204 ± 11 ^c	183 ± 9 ^{b,c}	130 ± 12 ^{a,c}	120 ± 12 ^{a,b,c}	131 ± 11 ^{a,b,c}
	E	201 ± 14 ^d	199 ± 14 ^d	153 ± 19 ^{a,b,d}	116 ± 16 ^{a,d}	96 ± 11 ^{a,b,d}	110 ± 9 ^{a,b,d}
	H	145 ± 8 ^{c,d}	153 ± 9 ^{c,d}	103 ± 17 ^{a,c,d}	93 ± 11 ^{a,c,d}	73 ± 16 ^{a,c,d}	90 ± 10 ^{a,c,d}
SI (ml/kg)	I	1.15 ± 0.09	1.15 ± 0.09	1.14 ± 0.07	0.96 ± 0.12 ^a	0.94 ± 0.13 ^a	1.02 ± 0.13
	E	1.12 ± 0.06	1.07 ± 0.07	0.91 ± 0.09 ^a	0.85 ± 0.10 ^a	0.73 ± 0.08 ^a	0.83 ± 0.05 ^a
	H	0.88 ± 0.09	0.91 ± 0.07	0.71 ± 0.11 ^a	0.75 ± 0.08	0.63 ± 0.10 ^a	0.76 ± 0.05
SVR (dynes·sec·cm ⁻⁵)	I	6484 ± 512	5379 ± 253	4383 ± 350 ^a	7539 ± 268 ^a	5591 ± 378	5511 ± 503
	E	4800 ± 612	4356 ± 569	4208 ± 491	6636 ± 1110 ^a	5065 ± 459	5404 ± 698
	H	6543 ± 543	5543 ± 538	5211 ± 409 ^a	6290 ± 275	5043 ± 372 ^a	5542 ± 471
LVSW (g·m)	I	9.6 ± 0.7 ^{b,c}	8.8 ± 0.7 ^{b,c}	6.3 ± 0.6 ^{a,b,c}	6.4 ± 0.8 ^{a,b,c}	4.4 ± 0.7 ^{a,b,c}	5.2 ± 0.9 ^{a,b,c}
	E	6.6 ± 0.7 ^{b,d}	5.6 ± 0.5 ^{a,b}	3.6 ± 0.6 ^{a,b,d}	3.9 ± 0.7 ^{a,b}	2.3 ± 0.4 ^{a,b}	3.1 ± 0.4 ^{a,b}
	H	5.1 ± 0.6 ^{c,d}	5.0 ± 0.7 ^c	2.1 ± 0.8 ^{a,c,d}	3.2 ± 0.8 ^{a,c}	1.8 ± 0.6 ^{a,c}	2.8 ± 0.8 ^{a,c}
PVR (dynes·sec·cm ⁻⁵)	I	516 ± 43	591 ± 34	558 ± 71	758 ± 110	772 ± 169	683 ± 142
	E	573 ± 47	578 ± 68	669 ± 78	886 ± 136	874 ± 121	982 ± 171
	H	835 ± 83	874 ± 88	943 ± 116	1117 ± 135	1275 ± 418	1370 ± 386 ^a
Hct (%)	I	30.4 ± 1.1	30.2 ± 1.5	27.8 ± 1.6 ^a	28.0 ± 1.8 ^a	26.6 ± 1.9 ^a	26.2 ± 1.8 ^a
	E	30.0 ± 1.3	29.2 ± 1.5	27.0 ± 1.3 ^a	26.2 ± 1.2 ^a	24.8 ± 1.2 ^a	24.0 ± 1.3 ^a
	H	31.6 ± 2.2	31.2 ± 3.0	29.0 ± 2.2 ^a	28.0 ± 2.7 ^a	26.4 ± 2.4 ^a	26.2 ± 2.6 ^a

Data are mean ± SE. *n* = 5 for each group.

Abbreviations: N, nifedipine; P, propranolol; Ca, calcium chloride; I, isoflurane; E, enflurane; H, halothane; HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; maxLVdP/dt, maximum rate of rise of the left ventricular pressure; CI, cardiac index; SI, stroke index; SVR, systemic vascular resistance; LVSW, left ventricular stroke work; PVR, pulmonary vascular resistance; Hct, hematocrit.

^a*P* < 0.05 compared with 0.75 MAC without drugs.^b*P* < 0.05 between I and E.^c*P* < 0.05 between I and H.^d*P* < 0.05 between E and H.

ing enflurane or halothane anesthesia. This difference in blood pressure was related to the severe myocardial depression that occurred with enflurane and halothane; CI was 20% greater with isoflurane when compared with enflurane and 40% greater when compared with halothane.

In the presence of continuous infusions of both propranolol and nifedipine and 1.25 MAC level of anesthesia, the administration of 10 mg/kg CaCl₂ increased CI and max LV dP/dt during all three anesthetics. However, CaCl₂ did not return these values to baseline levels (Fig. 2 and Table 1). Systemic vascular resistance was unchanged by CaCl₂ administration. The observed hemodynamic changes after bolus administration of CaCl₂ were transient, lasting <5 min in all monkeys.

Discussion

Our results suggest that the administration of nifedipine alone or nifedipine plus propranolol causes less myocardial depression during isoflurane anesthesia than during either enflurane or halothane anesthesia. In the study group, isoflurane anesthesia alone at 0.75 MAC was associated with a higher MAP, resulting from a higher CI than with halothane and a greater arterial vasomotor tone than with enflurane. Systemic vascular resistance was similar during isoflurane and halothane anesthesia. Isoflurane is generally considered to be a more potent vasodilator than halothane (18), but this may not always be the case. For example, Mallow et al. (19) compared the effects of halothane and isoflurane in patients undergoing coronary artery

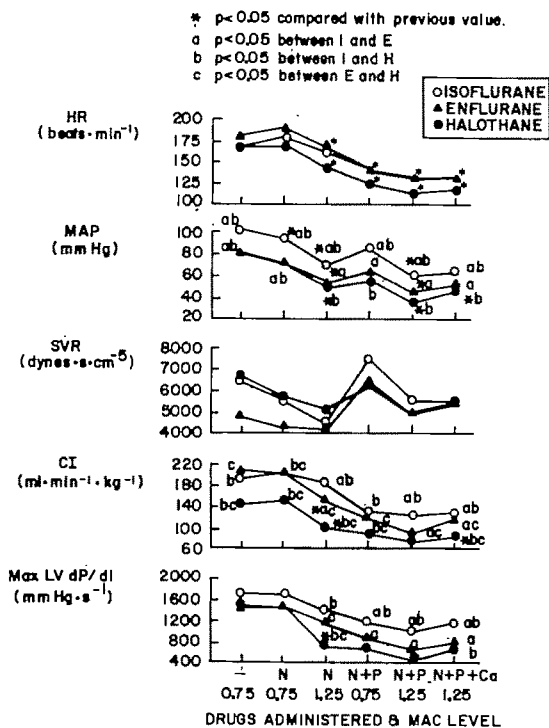


Figure 2. Drug-induced changes in HR, MAP, SVR, CI, and max LV dP/dt during infusion of nifedipine (N) and propranolol (P), the bolus injection of and calcium chloride (Ca). Open circles, isoflurane (I); filled triangles, enflurane (E); filled circles, halothane (H). Mean values are shown. $n = 5$ for each group. * $P < 0.05$ compared with previous value. * $P < 0.05$ between I and E. * $P < 0.05$ between I and H. * $P < 0.05$ between E and H.

bypass surgery and reported similar SVR in both groups. Although isoflurane is also generally considered to be a milder myocardial depressant than halothane or enflurane, this may not be true for isoflurane at doses <1 MAC concentration (20).

At 0.75 MAC anesthesia, nifedipine was well tolerated during all three types of anesthesia (Fig. 2). The small decrease in MAP when nifedipine was infused during isoflurane anesthesia was presumably secondary to vasodilation, and HR, CI, max LV dP/dt remained unchanged. Other studies in awake and lightly anesthetized animals showed nifedipine to increase CO and HR significantly (7,9). However, the hemodynamic response to nifedipine may be variable. For example, Springman et al. (10) found lesser increases in HR and CO in dogs given nifedipine during 1% halothane anesthesia than during morphine- N_2O - O_2 anesthesia. The hemodynamic response to nifedipine during anesthesia also depends on the depth of anesthesia at the time nifedipine is administered (9). Other factors, such as intravascular volume status, may also be important.

At higher levels (1.25 MAC) of anesthesia the in-

Table 2. Plasma Propranolol Levels (ng/ml) in Monkeys during Isoflurane, Enflurane, and Halothane Anesthesia with Infusions of Nifedipine and Propranolol and after Calcium Chloride Administration

	Drug given (MAC)		
	N + P (0.75)	N + P (1.25)	N + P + Ca (1.25)
Isoflurane	25.8 $\pm$ 8.7	22.4 $\pm$ 7.4	19.4 $\pm$ 6.2
Enflurane	35.0 $\pm$ 7.1	32.6 $\pm$ 7.5	29.3 $\pm$ 5.9
Halothane	27.1 $\pm$ 7.3	26.6 $\pm$ 6.1	28.4 $\pm$ 7.4

Data are mean $\pm$ SE. $n = 5$ for each group.

Abbreviations: N, nifedipine; P, propranolol; Ca, calcium chloride.

fusion of nifedipine did not alter CI during isoflurane anesthesia, but decreased CI with enflurane and halothane. The hemodynamic stability at higher concentrations of isoflurane during nifedipine administration is consistent with the fact that isoflurane at higher concentrations causes less cardiac depression in vivo than do other inhalation anesthetics when administered alone or together with depressant drugs like propranolol (10,21) or verapamil (4-6,9).

β -Adrenergic blockade in normal humans in the absence of anesthesia decreases heart rate, contractility, and systolic blood pressure only slightly (22). The magnitude of these changes depends on the prior level of sympathetic activity. In patients with coronary artery disease, 0.1 mg/kg IV propranolol does not decrease CI, whereas a dose of 0.15 mg/kg does. Despite this decrease in CI, MAP is maintained by an increase in SVR, presumably because of the unopposed α -adrenergic activity (23,24).

Studies on hemodynamic interactions between inhalation anesthetics and propranolol have shown that myocardial depression and a reduction in HR occur. In 1975, Philbin and Lowenstein (25) reported a 17% decrease in CO and a 17% decrease in HR after 0.5 mg/kg propranolol during 1 MAC isoflurane anesthesia in dogs. In 1976, the same authors (21) reported a 10% decrease in CO and a 10% decrease in HR after the same dose of propranolol at the same level of isoflurane anesthesia in dogs. In 1977, Horan et al. (26) found that 0.3 mg/kg propranolol during 1 MAC of isoflurane decreased CO by 8% and HR by 6%.

Propranolol in the dog causes more significant cardiovascular depression during enflurane anesthesia than during halothane anesthesia (27). Additive depressive effects occur only when propranolol is given during halothane anesthesia (28-31).

In our study, HR, CI, and max LV dP/dt decreased during propranolol infusions at rates calculated to be sufficient to give plasma levels known to produce about 75% β -adrenergic blockade in humans; SVR increased only in the isoflurane and enflurane groups,

and then only at 0.75 MAC. The decrease in SVR at 1.25 MAC might have occurred because at higher anesthetic levels sympathetic nervous stimulation, which produces α effects, was depressed. It is also possible that halothane and higher levels of isoflurane and enflurane (1.25 compared with 0.75 MAC) in the presence of nifedipine attenuate the increased vascular smooth muscle tone caused by unopposed α -adrenergic activity.

When we compare the results of our study with previous studies (21,25-31), we notice that in our study propranolol caused a greater than expected hemodynamic depression after pretreatment with nifedipine, even at low levels of inhalation anesthesia. For example, at 0.75 and 1.25 MAC of isoflurane and with nifedipine pretreatment, CI decreased 36 and 35%, and HR decreased 22 and 19%, after nifedipine alone and after nifedipine plus propranolol. This decrease in CI suggests that nifedipine had a depressant effect on the cardiovascular system that may have been synergistic with the depressant effects of propranolol. Inhalation anesthetics, calcium channel-blocking agents, and β -adrenergic blocking agents all decrease myocardial contractility, probably by different mechanisms, yet all result in a decrease in intracellular calcium levels (32). The interaction of all three agents simultaneously, each acting through a different mechanism, may have decreased intracellular calcium to very low levels, thereby causing a synergistic depression in cardiac performance.

Winniford et al. (2) reported that the combination of nifedipine and propranolol causes less hemodynamic depression than does the combination of verapamil and propranolol in awake patients with stable angina. However, if one extrapolates our study to humans, even patients receiving the "safer" combination of nifedipine and propranolol may be very sensitive to low concentrations of inhalation anesthetics, especially enflurane and halothane. At 1.25 MAC, the higher MAP and CI in the isoflurane group compared with the enflurane and halothane groups during calcium channel and β -adrenergic blockade also suggests a greater margin of hemodynamic safety with isoflurane in this animal preparation, and possibly also in patients with decreased cardiovascular reserve. CI and max LV dP/dt were greater with isoflurane (1.25 MAC) in the presence of nifedipine and propranolol, than during enflurane or halothane anesthesia (1.25 MAC) at the same measured afterload. This finding is consistent with the observations that at higher isoflurane concentrations there is some degree of cardiac sympathetic stimulation (20).

Bolus IV administration of CaCl_2 (10 mg/kg) partially reversed the myocardial depression induced by

nifedipine and propranolol (Table 1 and Fig. 2). This finding suggests that some of the observed cardiac depression from the combination of nifedipine and propranolol during anesthesia may be reversible by increasing the serum ionized calcium level. A higher plasma ionized calcium concentration may increase the intracellular influx of calcium, thereby increasing myocardial contractility (32). Indeed, it has been shown that CaCl_2 increases CI and stroke index in halothane-anesthetized patients (33). Calcium chloride also decreases the direct myocardial depressant effects of verapamil, nifedipine, and diltiazem during halothane anesthesia, with minimal changes in SVR (11). We also noted that SVR was unchanged after CaCl_2 administration. Therefore, if it is necessary to increase systemic blood pressure after nifedipine and propranolol administration during inhalation anesthesia, and decreasing anesthetic concentration is ineffective, it may be reasonable to use an α -adrenergic agonist before or instead of CaCl_2 administration. Likewise, a β -adrenergic agonist infusion may be preferred for reversal of severe cardiovascular depression if decreasing anesthetic concentration is ineffective, because CaCl_2 infusion only minimally and transiently increases myocardial contractility (34).

The small number of monkeys we studied is a possible limitation of this study. However, because the selection of anesthetic agent was randomized and each animal served as its own control for subsequent drug administration, variability of responses was minimized. Also, control did not have any time-dependent hemodynamic changes at equal MAC levels of anesthesia.

Last, plasma nifedipine levels were not measured. In the presence of halothane and enflurane anesthesia, acute loading with propranolol and verapamil decreases metabolism of these agents, presumably because of decreases in cardiac output and hepatic blood flow (5,6,35). We also found that propranolol levels were slightly, although not significantly, higher in the enflurane and halothane groups than in the isoflurane group. The same might have been true of nifedipine plasma levels. Therefore, differences in hemodynamic depression observed between anesthetic groups may have been due in part to differences in plasma levels of propranolol and nifedipine. Also, Merin et al. (36), have shown that with inhalation anesthetics chronic administration of verapamil causes less hemodynamic depression than acute loading, even though serum concentrations of verapamil are similar. This finding should alert us to the possibility that when nifedipine and propranolol are administered acutely during inhalation anesthesia, lower doses of these drugs should be given.

In summary, in unstimulated, healthy monkeys, acute loading with nifedipine with and without propranolol exerts a greater myocardial depressant effect in the presence of enflurane or halothane than in the presence of isoflurane. In this setting the cardiovascular effects of propranolol combined with nifedipine seem to be synergistic and are only partially and temporarily reversed by CaCl_2 administration. If our results can be extrapolated to humans, they suggest that patients being treated with nifedipine and propranolol should be given inhalation anesthetics most carefully, especially when halothane or enflurane are employed.

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Spinal Anesthesia with Hyperbaric Lidocaine and Bupivacaine: Effects of Epinephrine on the Plasma Concentration Profiles

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BURM AGL, VAN KLEEF JW, GLADINES MPRR, VAN DUINEN M, SPIERDIJK J. Spinal anesthesia with lidocaine and bupivacaine: effects of epinephrine on the plasma concentration profiles. *Anesth Analg* 1987;66:1104-8.

The effects of epinephrine on the plasma concentration profiles and some derived pharmacokinetic parameters were studied after subarachnoid injection of hyperbaric lidocaine and bupivacaine solutions. Addition of epinephrine to the local anesthetic solution reduced the mean peak plasma concentration of lidocaine from 526 to 376 ng/ml, but did not

significantly reduce the mean peak plasma concentration of bupivacaine (70 vs 56 ng/ml). Epinephrine did not affect the times at which the peak concentrations were reached, the terminal half-lives, or the total plasma clearances. The observed effects of epinephrine on the peak plasma concentrations are consistent with the vascular activity of lidocaine and bupivacaine, respectively.

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHETICS, LOCAL—lidocaine, bupivacaine. PHARMACOKINETICS—lidocaine, bupivacaine.

The clinical usefulness of addition of epinephrine to local anesthetic solutions for subarachnoid administration is controversial. Several investigators reported significant but widely varying increases in the duration of the spinal block when epinephrine was added to solutions of tetracaine and bupivacaine (1-3). The differences in the results could not be accounted for by differences in the amounts of epinephrine that were added (0.1-0.5 mg). On the other hand, recent investigations indicated that addition of epinephrine to solutions of lidocaine and bupivacaine provides little or no clinically useful prolongation of the action, whereas addition of epinephrine to tetracaine solutions only produces a useful prolongation in the lower segments (4-7).

It is generally assumed that epinephrine prolongs the duration of action of local anesthetics by reducing local blood flow, thereby slowing the systemic absorption and increasing the neuronal uptake of the local anesthetic agent (8,9). The possible contribution

of a direct pharmacologic action of epinephrine (10,11) on spinal nerve structures remains to be clarified. Insofar as the action of epinephrine is caused by an effect on local perfusion, the degree to which the desired effects are obtained is dependent on the vasoactive properties of the local anesthetic itself, which may vary with the type and dose of the local anesthetic and with the site of injection (9,12-14). In view of the vasoactive effects of local anesthetics after subarachnoid administration (12-14), one might expect a more profound slowing of the systemic absorption by addition of epinephrine to lidocaine or tetracaine solutions than by addition to bupivacaine solutions. However, conclusive data are lacking. Axelsson and Widman (15) reported considerably lower peak plasma concentrations, but no change in the times at which these were reached, after subarachnoid administration of lidocaine solutions with epinephrine compared to plain lidocaine solutions. On the other hand, addition of epinephrine to lidocaine solutions for subarachnoid injection in Rhesus monkeys (16) and dogs (17) had no significant effect on either the peak plasma concentrations or the corresponding peak times. Data on the effects with other local anesthetics are lacking. Therefore we investigated the effects of epinephrine on the plasma concentration profiles after subarachnoid administration of hyperbaric lidocaine and bupivacaine solutions.

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Table 1. Mean Age, Body Weight, Height, and Male/Female Ratio in Each Group of Patients^a

	Lidocaine, plain (n = 10)	Lidocaine plus epinephrine (n = 10)	Bupivacaine, plain (n = 10)	Bupivacaine plus epinephrine (n = 10)
Age (yr)	35 ± 11	33 ± 8	29 ± 8	28 ± 10
Body weight (kg)	75 ± 13	79 ± 11	82 ± 18	78 ± 15
Height (cm)	174 ± 7	178 ± 8	182 ± 9	178 ± 9
Male/female ratio	7/3	7/3	8/2	8/2

^aValues are mean ± SD, where appropriate.

Methods

Forty healthy (ASA status I) patients, between 20 and 50 yr old and scheduled for minor general or orthopedic surgery of the lower limbs, participated in the investigation. The study was approved by the Committee on Medical Ethics of the University Hospital and informed consent was obtained from each patient.

Local anesthetic solutions studied were hyperbaric (75 mg/ml glucose) 5% lidocaine (dose 100 mg) and hyperbaric (80 mg/ml glucose) 0.5% bupivacaine (dose 15 mg). To these solutions was randomly added 0.15 ml (0.15 mg) of a fresh 1:1000 epinephrine solution.

Anesthetic Procedure

The patients were premedicated with lorazepam 2 mg sublingually about 1.5 hr, and atropine 0.5 mg intramuscularly about 0.5 hr before induction of spinal anesthesia. A central venous catheter was introduced into a basilic or cephalic vein after local infiltration with lidocaine or bupivacaine (not the agent to be studied). The catheter was advanced until the tip was located in the central conduit, but at least 6 cm proximal to the junction of the azygos vein and the superior vena cava. The correct location of the tip of the catheter was verified using roentgenograms of the thorax. In addition an arterial cannula was introduced into the radial artery in 12 patients. Lumbar puncture was performed with the patient sitting. After local infiltration with procaine a 25-g spinal needle was introduced into the subarachnoid space via the third lumbar vertebral interspace. After a free flow of clear cerebrospinal fluid was obtained and after aspiration, the local anesthetic solution was injected, without barbotage, at a rate of approximately 0.15 ml/sec. Immediately after the injection the patient was placed in the supine horizontal position. During the operation the patient remained in this position. Sedative drugs were not administered. Postoperative pain was controlled with methadone or paracetamol.

The level of analgesia was assessed using pinpricks and the degree of motor blockade was assessed using

a modified Bromage classification. Both assessments were made bilaterally by an independent investigator who, along with the patient, was unaware of whether or not epinephrine had been added to the local anesthetic solution.

Pharmacokinetic Investigations

Central venous blood samples were collected before the subarachnoid injection, at 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, and 150 min, and subsequently every hour for 12 hr after the subarachnoid injection. In 12 patients arterial samples were collected simultaneously for 4 hr after the injection to detect any arterio-venous differences in the concentrations of the local anesthetic. Blood samples were transferred into heparinized centrifuge tubes. After centrifugation, plasma was collected and stored at -20°C. Local anesthetic concentrations were determined using capillary gas chromatography with solid injection and nitrogen-selective detection according to procedures described elsewhere (18,19), with few modifications (20). The individual peak plasma concentrations ($C_{\max}$) and the corresponding peak times ($t_{\max}$) were determined. Terminal half-lives ($t_{1/2,Z}$) were calculated from the rate constants (k_Z) obtained by linear regression analysis of the log-linear part of the plasma concentration-time curve:

$$t_{1/2,Z} = 0.69/k_Z.$$

The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule including extrapolation to infinity (21). The total plasma clearance (CL) was calculated according to the equation:

$$CL = D/AUC,$$

where D is the administered dose.

Statistical Analysis

All data are presented as mean ± SD, where appropriate. A two-sample *t*-test was used to test the effects

Figure 1. Typical plasma concentration curves obtained after subarachnoid administration of a hyperbaric 5% lidocaine solution (100-mg dose) and a hyperbaric 0.5% bupivacaine solution (15-mg dose). Both solutions contained 0.15 mg epinephrine. During the first 240 min after the administration, both arterial and central venous blood samples were collected.

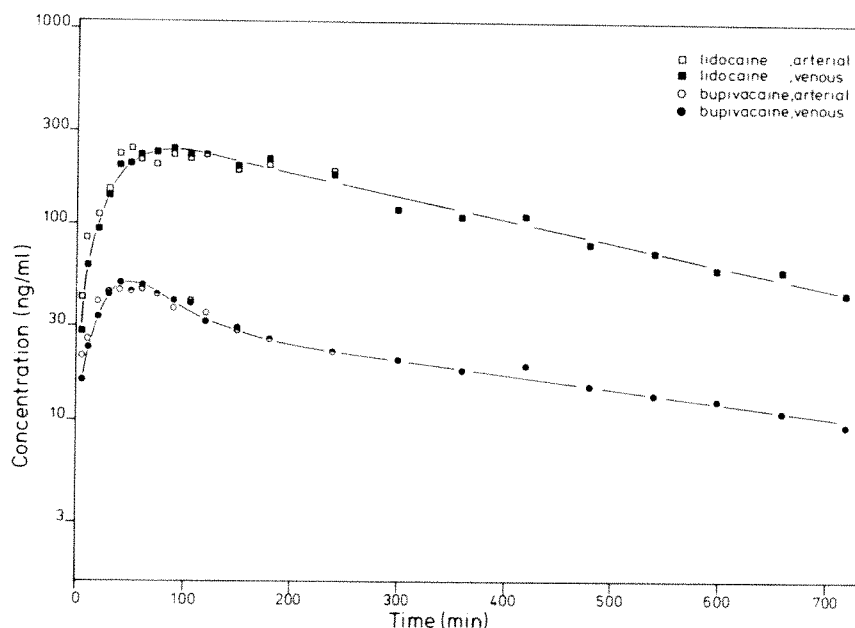


Table 2. Pharmacokinetic Data after Subarachnoid Administration of Hyperbaric 5% Lidocaine and Hyperbaric 0.5% Bupivacaine Solutions^a

	Lidocaine, plain (n = 10)	Lidocaine plus epinephrine (n = 10)	Bupivacaine, plain (n = 10)	Bupivacaine plus epinephrine (n = 10)
t _{max} (min)	71 ± 29	58 ± 24	62 ± 33	59 ± 27
C _{max} (ng/ml)	526 ± 141 ^b	376 ± 108 ^b	70 ± 32	56 ± 15
T _{1/2,α} (min)	131 ± 37	163 ± 55	280 ± 86	249 ± 66
Clearance (ml/min)	797 ± 220	841 ± 228	606 ± 169	590 ± 130

^aValues are mean ± SD.

^bDifference between lidocaine plain and lidocaine plus epinephrine: $P < 0.01$.

of epinephrine. A value of $P < 0.05$ was regarded as the minimal level of statistical significance.

Results

There were no significant differences in age, body weight, height and ratio of males to females between the groups of patients who received a local anesthetic solution with epinephrine and those who received a plain solution (Table 1).

Epinephrine did not alter the onset of analgesia or motor blockade. Nor did it affect the upper levels of analgesia, which were around T-6 with both lidocaine solutions and around T-7 and T-5 with the plain and the epinephrine-containing bupivacaine solutions, respectively. Addition of epinephrine to lidocaine solutions resulted in a prolongation of the two-segment regression time, as well as the time until total recovery from analgesia and motor blockade. Addition of epinephrine to bupivacaine solutions did not result in a

prolongation of the spinal block. Full details of the effects of epinephrine on the onset, the quality, and the duration of the spinal block have been described elsewhere (20).

Lidocaine and bupivacaine concentrations in arterial plasma samples, collected 5 min after administration of the local anesthetic solutions, were systematically higher than the corresponding concentrations in central venous plasma samples in all except one patient. However, the peak plasma concentrations and the peak times derived from the arterial and central venous plasma concentration curves were similar (Fig. 1).

The mean peak plasma concentration of lidocaine after administration of a solution with epinephrine was significantly lower than the mean value after administration of a plain solution (376 vs 526 ng/ml), but the corresponding peak times (58 and 71 min, respectively) did not differ significantly. Epinephrine did not affect the peak concentration of bupivacaine

or the time at which the peak concentration of bupivacaine was reached (Table 2). The values of the terminal half-lives of lidocaine and bupivacaine were approximately 150 and 260 min, respectively, and were independent of the addition of epinephrine. The mean clearance values were approximately 820 and 600 ml/min for lidocaine and bupivacaine, respectively, and were also not affected by the addition of epinephrine.

Discussion

To interpret the effects of epinephrine on the plasma concentration profiles of different local anesthetics, it is essential that the extent of the neural blockade is fixed, so that effects of differences in sympathetic denervation that might interfere with the local perfusion are avoided. In the present study, with clinically used lidocaine (5%) and bupivacaine (0.5%) solutions of different anesthetic strength, this was achieved by injecting different volumes of the lidocaine (2 ml) and bupivacaine (3 ml) solutions. To these solutions a fixed amount of epinephrine was added. Consequently, the concentrations of epinephrine in the lidocaine solutions (0.0698 mg/ml) was higher than in the bupivacaine solutions (0.0476 mg/ml). Addition of a fixed amount of epinephrine, rather than addition to a fixed concentration, is common clinical practice. This strategy is based on the assumption that at a given speed of injection the solution will be dispersed into a similar volume of cerebrospinal fluid (CSF), so that after injection and dilution with CSF, the CSF concentration of epinephrine will be similar, irrespective of the injected volume.

The results of this study confirm the observation of Axelsson and Widman (15) that addition of epinephrine to hyperbaric lidocaine solutions reduces the peak plasma concentration without altering the time at which this is reached. On the other hand, epinephrine did not affect either the peak plasma concentration of bupivacaine or the time at which the peak concentration of bupivacaine was achieved. The disparity in the results obtained with both local anesthetics is consistent with the difference in their effects on the spinal cord and spinal dural blood flows (local perfusion). Kozody et al. (13,14), for example, have shown in a dog model that after subarachnoid administration lidocaine increases the local perfusion, whereas bupivacaine decreases the local perfusion. Addition of epinephrine to lidocaine solutions counteracts the increase of the local perfusion and thereby slows the systemic absorption, which explains the reduction of the peak plasma concentration. Addition of epinephrine to bupivacaine solutions causes min-

imal changes in the local perfusion and in the plasma concentration profile.

The effects of epinephrine on the plasma concentration profiles are also consistent with the clinical observations of both Chambers et al. (4,5) and Burn (20). With lidocaine, the slowing of the systemic absorption, which promotes the neuronal uptake of the local anesthetic, is accompanied by a small prolongation of the duration of action. With bupivacaine, epinephrine alters neither the rate of absorption nor the duration of action.

The clinical usefulness of addition of epinephrine to lidocaine and bupivacaine solutions is questionable. In the studied situation, i.e., after administration of a hyperbaric solution with the patient in the sitting position, most of the local anesthetic (and epinephrine) will remain in the lumbosacral region. In this situation, the prolongation of the duration of action, if present, is minimal, mainly confined to the lower lumbar and sacral segments, and of marginal clinical significance (4,5,7,20). Also, a reduction of the peak plasma concentration is redundant, because the plasma concentrations after subarachnoid administration of both lidocaine and bupivacaine are far below the toxic threshold concentrations, even if epinephrine is not added. The clinical usefulness of epinephrine in other situations such as after injection of a hypobaric solution, in which a larger portion of the injected dose may reach the upper lumbar and thoracic regions, remains to be clarified.

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Antagonism of Postoperative Opioid-Induced Respiratory Depression: Nalbuphine Versus Naloxone

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BAILEY PL, CLARK NJ, PACE NL, STANLEY TH, EAST KA, van VREESWIJK H, van de POL P, CLISSOLD MA, ROZENDAAL W. Antagonism of postoperative opioid-induced respiratory depression: nalbuphine versus naloxone. *Anesth Analg* 1987;66:1109-14.

The authors compared naloxone and nalbuphine as antagonists of opioid-induced respiratory depression to determine the relative efficacies and safety of the two agents. In a double-blind, randomized fashion, 90 anesthetized patients received a mean dose of 25 µg/kg fentanyl during surgery. Inadequate spontaneous respirations at the end of anesthesia were treated with either naloxone 0.08 mg or nalbuphine 2.5 mg IV every 2 min while heart rate (HR), systolic and diastolic blood pressures (SBP, DBP), respiratory rate (RR), and tidal volume (TV) were measured at 2-min intervals. Arterial blood samples for analysis of PaCO₂, PaO₂, and pH were drawn when spontaneous ventilation resumed, and 30 and 60 min later. Narcotic antagonism and respiration were deemed adequate when TV was ≥ 4 ml/kg and RR ≥ 8 breaths/min. Heart rate, SBP, DBP, TV and RR were recorded, as were the occurrence of renarcotization (RR < 8)

and analgesic requirements every 5 min during the recovery room stay. Sixty of 90 patients required narcotic antagonism at the end of surgery. No patient required more than three doses (0.24 mg) of naloxone or four doses (10 mg) of nalbuphine. Both antagonists produced similar and moderate increases in SBP and HR while restoring adequate spontaneous ventilation. There were no significant differences in TV, RR, or arterial blood gases (ABGS) between the two groups after narcotic reversal. Five patients in whom respiratory depression was antagonized with naloxone and two receiving nalbuphine became renarcotized 30-90 min after entering the recovery room (not statistically different), but patients given naloxone required analgesics for pain significantly more often than those reversed with nalbuphine (12 vs 5). With the exception of providing better immediate postoperative analgesia, small doses of nalbuphine and naloxone are equally effective and safe antagonists of opioid-induced respiratory depression after operation.

Key Words: ANTAGONISTS—naloxone, nalbuphine. NARCOTICS—nalbuphine.

Nalbuphine, a mixed agonist-antagonist opioid, has recently been evaluated as an alternative to naloxone for reversal of narcotic-induced respiratory depression (1-5). Some investigators have suggested that nalbuphine administration after intraoperative opioids can restore adequate spontaneous ventilation without antagonizing analgesia (1-3). Unfortunately, side effects, e.g. hypertension and pain, have occurred after nalbuphine and have been reminiscent of problems

associated with naloxone (4,5). We are unaware of any double-blind, randomized study comparing naloxone and nalbuphine as antagonists of opioid-induced respiratory depression in the immediate postoperative period, and decided to perform such an investigation in patients receiving large doses of fentanyl during operation.

Methods

The study was approved by the University of Utah Medical Center Institutional Review Board and patients gave informed consent before being enrolled in the study. Ninety ASA I-II patients without a history of opioid analgesic use and scheduled for elective general, orthopedic, or gynecologic surgery served as the experimental subjects. Preoperative medication was ordered by the anesthesiologist caring for the patient.

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Table 1. Demographics and Preoperative Vital Signs

	Age (yr)	Height (cm)	Weight (kg)	Female/ male	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)
Naloxone	36 ± 16	169.4 ± 10.4	70.6 ± 14.3	9/21	120 ± 14	75 ± 10	75 ± 12
Nalbuphine	40 ± 15	168.7 ± 10.6	71.3 ± 15.2	12/18	123 ± 12	78 ± 10	76 ± 7

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
All values mean ± SD.

Before surgery a peripheral IV catheter was inserted in a hand or arm vein and an infusion begun with dextrose 5% in Ringer's lactate solution. In the operating room a three-lead ECG, automatic blood pressure cuff (Spacelabs), a pulse oximeter (Nelcor), and a precordial stethoscope were applied while the patient breathed 100% oxygen. Anesthetic induction proceeded with a defasciculating dose of curare 3 mg IV, fentanyl 15 µg/kg IV over 2 min, and thiopental 1–4 mg/kg IV as needed to produce loss of consciousness. Succinylcholine 1.5 mg/kg IV was used for muscle relaxation, and all patients had their trachea intubated with an endotracheal tube. Anesthesia was maintained with 40% oxygen, 60% nitrous oxide, and intermittent boluses of fentanyl, 50 µg every 15 min. Isoflurane, 0.1–1.0% was used to prevent increases in blood pressure greater than 25% of baseline levels, and nondepolarizing muscle relaxants were used if clinically indicated.

Patients were mechanically ventilated to maintain an end-tidal CO₂ of 40 ± 2 mm Hg (Hewlett-Packard 47210 A Capnometer). Isoflurane was discontinued 5–10 min before the end of surgery. Muscle relaxation was reversed with edrophonium (0.5–1.5 mg/kg) and atropine (0.5–1.0 mg) IV until patients could sustain a tetanus and normal train-of-four to peripheral nerve stimulation. Nitrous oxide was discontinued and mechanical ventilation with 100% oxygen continued for 2 min. After this, mechanical ventilation ceased and heart rate (HR), systolic and diastolic blood pressures (SBP, DBP), respiratory rate (RR), and tidal volume (TV) (Narkomed 2A respirometer) were measured and recorded, and considered as baseline values for study purposes (time zero). Patients were then manually ventilated at a rate of one breath/min (TV approximately 500 ml) or more if needed to maintain a PETCO₂ ≤ 55 mm Hg and an oximetric hemoglobin saturation ≥ 90%.

If apnea persisted for 2 min or spontaneous ventilation was inadequate (TV < 4 ml/kg or RR < 8), the above measurements were repeated (time 2 min) and either naloxone (Nx) or nalbuphine (Nb) was given IV in a double-blind, randomized manner. One dose of either antagonist equalled 1 ml and the concentrations were Nx 0.08 mg/ml and Nb 2.5 mg/ml. These

doses were chosen on the basis of our clinical experience, which indicated they were equipotent in their ability to produce opioid antagonism and would be large enough to produce adequate reversal in a clinically acceptable time frame, yet small enough to minimize the occurrence of abrupt arousal and hemodynamic changes. Every 2 min the above measurements were repeated and the same dose of antagonist was administered until spontaneous ventilation was adequate (TV ≥ 4 ml/kg and RR ≥ 8 breaths/min), after which the patient was extubated. Patients were then transported to the recovery room.

Arterial blood samples for blood gas analysis (Radiometer Copenhagen ABL-2) were obtained via percutaneous puncture of a radial artery when spontaneous ventilation resumed during reversal, and 30 and 60 min later. In the recovery room HR, SBP, DBP, RR, and TV were recorded every 5 min. Renarcotization in the recovery room, defined as a RR < 8 in a nonstimulated patient, was treated with naloxone, 0.08 mg IV. Analgesics (morphine 2 mg IV or meperidine 25 mg IV) were administered by the recovery room nurses when patients spontaneously reported pain more than once in a 5-min period or reported severe pain. Patients were discharged from the recovery room when oriented to day, place, and person, when blood pressure and heart rate were stable (within 20% of preanesthetic values), and when the spontaneous, quiet respiratory rate was ≥ 8 breaths/min for at least 60 min after entering the recovery room.

Data were analyzed for statistical significance using Hotelling *t*-square, unpaired *t*-tests, and the χ^2 -test. The BMDP statistical package was used (BMDP Statistical Software, Department of Biomathematics, UCLA, Berkeley, CA: University of California Press, 1981, module P3D, P4F). Probability values < 0.05 were considered statistically significant.

Results

Ninety patients gave informed consent and were enrolled into the study protocol, but only 60 of them required opioid antagonism at the end of surgery. Thirty patients received naloxone and an equal number received nalbuphine. There were no differences

Table 2. Study Drug Doses and Time Intervals

	Fentanyl dose ($\mu\text{g/kg}$)	Number of antagonist doses (ml)	Duration of anesthesia (min)	F $\rightarrow$ R ^a interval (min)	R $\rightarrow$ E ^b interval (min)	Recovery time (min)
Naloxone	25.0 $\pm$ 8.6	1.8 $\pm$ 0.6	174 $\pm$ 81	22 $\pm$ 16	6 $\pm$ 2	92 $\pm$ 37
Nalbuphine	24.2 $\pm$ 5.5	2.3 $\pm$ 1.5	168 $\pm$ 66	24 $\pm$ 18	7 $\pm$ 3	95 $\pm$ 32

All values mean $\pm$ SD.

^aTime interval from last fentanyl dose to beginning of reversal.

^bTime interval from beginning of reversal to extubation.

between the Nx and Nb groups with respect to age, height, weight, gender distribution, and preoperative vital signs (Table 1). No patients given Nb and two patients given Nx had a diagnosis of hypertension on admission to the hospital; one was taking antihypertensive medication.

Patients in the two groups received similar preoperative medications consisting of a benzodiazepine or antihistamine and/or morphine. The two groups received comparable doses of fentanyl (Nx group, 25 $\pm$ 9 $\mu\text{g/kg}$; Nb group, 24 $\pm$ 6 $\mu\text{g/kg}$) and required similar doses (ml) of narcotic antagonist (Nx, 1.8 $\pm$ 0.6; Nb, 2.3 $\pm$ 1.5) (Table 2). This is equivalent to a total dose of 0.14 $\pm$ 0.05 mg of Nx and 5.75 $\pm$ 0.38 mg of Nb. The duration of anesthesia, the intervals from the last dose of fentanyl until the beginning of reversal and from the beginning of reversal until extubation, as well as the time spent in the recovery room, were not statistically different in the two groups (Table 2).

Compared with baseline values (time zero during reversal), similar, statistically significant changes in SBP, HR, RR, and TV occurred in both the Nx and Nb groups during reversal (Table 3) and during the recovery room period (Table 4). There were too few vital sign measurements at 8 and 10 min during the reversal period (often a transition period to the recovery room) for statistical analysis. Systolic blood pressure levels $>$ 170 mm Hg occurred only once during reversal (196 mm Hg, Nb group), while 11 patients (6 in Nx and 5 in the Nb group) had SBP levels $>$ 170 mm Hg in the recovery room. There was only one (5 min) SBP measurement $>$ 200 mm Hg (Nx group) during the recovery period. Sinus tachycardia (rate $>$ 100) during reversal (seven patients vs ten in the Nx and Nb groups, respectively) and recovery (nine patients vs seven in the Nx and Nb groups, respectively) occurred with similar frequency in both groups.

Renarcotization (RR $<$ 8) in the recovery room occurred in five patients given Nx and in two given Nb (not statistically different). Excluding patients who received analgesics in the recovery room (three pa-

tients in the Nx group who renarcotized had received morphine, 2 mg IV, in the recovery room) did not alter this result. Arterial pH, PaCO_2 and PaO_2 were similar in the two groups at the onset of spontaneous respiration, and 30 and 60 min later (Table 5). No patient had a $\text{PaCO}_2 >$ 69 mm Hg. Five patients in the Nx group vs only two patients in the Nb group had a $\text{PaCO}_2 >$ 50 mm Hg 30 and 60 min after the onset of spontaneous respiration. All patients were extubated $<$ 10 min after starting narcotic reversal. The difference in the number of patients requiring analgesics in the recovery room (12 in the Nx group vs 5 in the Nb group) was statistically significant (Table 6).

Discussion

The results of this study demonstrate that, when titrated in small doses, nalbuphine and naloxone are equally effective as postoperative antagonists of respiratory depression in patients given relatively large doses of fentanyl intraoperatively, and cause similar, moderate increases in systolic blood pressure and heart rate. The data also show that although renarcotization occurs with similar frequency after either drug, analgesics are required significantly more often after naloxone than after nalbuphine. Our findings suggest that nalbuphine is an acceptable alternative to naloxone for narcotic reversal and may be preferable in patients receiving large doses of opioids who are likely to have severe pain in the early postoperative period.

Postoperative respiratory depression is a major factor limiting the use and safety of intraoperative opioids. The need for an effective and safe opioid antagonist to reverse this side effect without complications persists in spite of more than three decades of research. Nalorphine (6) and levallorphan (7) were evaluated as narcotic antagonists in the 1950s, but both were deemed unreliable as agents for reversing or limiting opioid-induced respiratory depression (8). In the 1960s, naloxone was introduced as a better opioid antagonist (9); however, initial enthusiasm was tempered by clinical reports documenting serious problems (hyper-

Table 3. Vital Signs During Reversal

	Minutes after stopping mechanical ventilation			
	0	2	4	6
Naloxone				
SBP (mm Hg)	109 ± 19	110 ± 13	120 ± 22	129 ± 23 ^a
HR (beats/min)	62 ± 12	65 ± 14	79 ± 22 ^a	81 ± 23 ^a
RR (breaths/min)	—	—	6.9 ± 1.4 ^a	13.3 ± 1.6 ^a
TV (ml)	—	—	243 ± 57 ^a	553 ± 81 ^a
Nalbuphine				
SBP (mm Hg)	112 ± 13	114 ± 18	125 ± 19 ^a	137 ± 25 ^a
HR (beats/min)	60 ± 11	64 ± 13	76 ± 23	80 ± 12 ^a
RR (breaths/min)	—	—	6.7 ± 1.4 ^a	11.3 ± 1.8 ^a
TV (ml)	—	—	232 ± 66 ^a	504 ± 101 ^a

All values mean ± SD.

^aP < 0.05 compared with time zero.

tension, pulmonary edema, cardiac arrest) associated with its use (10–16). More recently, nalbuphine has been studied as an opioid antagonist using various dosage and administration schedules with differing degrees of success (1–5). We have previously reported that nalbuphine does not antagonize the respiratory depression produced by therapeutic doses of morphine in volunteers (15 mg/70 kg) (17). However, our clinical experience suggested that antagonism with nalbuphine provoked less hemodynamic change and postoperative pain than naloxone. The results of the present study indicate that naloxone and nalbuphine have similar efficacy and safety as narcotic antagonists. Why have opinions and reports differed concerning these two drugs?

One reason may be the dose of antagonist administered. The recommended dose for naloxone was initially 0.4–0.8 mg, and the last edition of a major American pharmacology text refers to these same doses as small (18). In addition, 0.4 mg or more of naloxone was used in eight of the ten cases reported where serious problems occurred (10,15–17). In contrast, we found that 0.08, 0.16 or, at most, 0.24 mg was all that was necessary for naloxone reversal of opioid-induced respiratory depression. In fact, only 3 of 30 patients (10%) required the highest dose of naloxone, 0.24 mg, used in this study. That these small doses are effective is even more impressive considering the dose of fentanyl our patients received (25 µg/kg).

Similarly, although some investigators have used up to 20 mg boluses of nalbuphine as an antagonist (1), we found that 10 mg was only necessary in 10% of our study patients. Usually 2.5, 5.0, or 7.5 mg of nalbuphine was sufficient to reverse the respiratory depression induced by large doses of fentanyl. Although it may be argued that a larger dose (10–20 mg) of nalbuphine will further decrease the occurrence of pain or renarcotization after reversal, we and others

Table 4. Vital Signs in the Recovery Room

	Minutes after entering the recovery room		
	5	30	60
Naloxone			
SBP (mm Hg)	145 ± 17	139 ± 19	132 ± 17
HR (beats/min)	88 ± 19	82 ± 20	82 ± 19
RR (breaths/min)	15 ± 4	14 ± 4	14 ± 5
TV (ml)	636 ± 225	583 ± 244	543 ± 209
Nalbuphine			
SBP (mm Hg)	146 ± 17	138 ± 20	128 ± 15
HR (beats/min)	89 ± 17	83 ± 18	80 ± 17
RR (breaths/min)	14 ± 3	14 ± 3	14 ± 4
TV (ml)	631 ± 326	607 ± 290	543 ± 197

All values mean ± SD.

(4) have not always found this to be true. Only 5 of 30 patients reversed with nalbuphine required analgesics in the recovery area (vs 12 of 30 in the naloxone group). Furthermore, the administration of small increments of morphine (2 mg) or meperidine (25 mg) provided satisfactory analgesia in patients who experienced severe pain after reversal or while in the recovery room.

The rate at which opioid antagonists are administered can also affect the outcome of opioid reversal. Because PaCO₂ increases rather slowly (3–6 mm Hg/min in apneic patients) (19), 2–3 min intervals between titrated doses of opioid antagonist are usually necessary to allow endogenous CO₂ to increase to adequate levels and stimulate respiration. If brain PCO₂ tensions are below the apneic threshold, opioid antagonists may produce consciousness before spontaneous respirations resume, resulting in abrupt arousal.

Patient selection may also be important in avoiding complications associated with opioid antagonism. Hemodynamic alterations, including hypertension, are not uncommon after antagonism of intraoperative opioids. There are data suggesting that patients with underlying cardiovascular disease are at increased risk for adverse effects during opioid antagonism (4,5). Although only 2 of the 60 patients in this study were known hypertensives, both these patients experienced the highest blood pressures recorded in our study. In addition, opioids and opioid antagonists can affect sympathetic tone by affecting transmission through sympathetic preganglionic neurons (20), and altering central sympathetic flow in certain hypertensive patients treated with clonidine (21). Although young, apparently healthy patients may also experience high blood pressures after naloxone or nalbuphine (Table 7), narcotic antagonism in hypertensive patients in particular may be difficult to achieve with-

Table 5. Arterial Blood Gas Tensions at the Onset of Spontaneous Respiration (SR), and 30 and 60 Minutes Later

	Onset SR	30 min	60 min	Range
Naloxone				
pH	7.30 ± 0.09	7.33 ± 0.09	7.32 ± 0.06	—
PCO ₂ (mm Hg)	49.2 ± 9.5	43.9 ± 9.4	42.5 ± 9.5	(19–65)
PaO ₂ (mm Hg)	209 ± 88	128 ± 53	102 ± 63	—
Nalbuphine				
pH	7.27 ± 0.06	7.32 ± 0.04	7.33 ± 0.03	—
PaCO ₂ (mm Hg)	50.2 ± 8.7	43.2 ± 5.2	42.5 ± 4.3	(30–69)
PaO ₂ (mm Hg)	183 ± 80	120 ± 52	84 ± 45	—

All values mean ± SD.

out significant hemodynamic alterations. Mechanically controlled ventilation should at least be considered as an alternative to opioid antagonism in selected patients where opioid-induced respiratory depression is excessive.

The occurrence of renarcotization was infrequent after narcotic antagonism with nalbuphine (2 of 30) in our study. Although this incidence was not significantly less than the incidence with naloxone (5 of 30), pharmacologic data and the longer elimination half-life for nalbuphine (3–4 hr) vs naloxone (30–60 min) (18) suggest that a study with a larger number of patients might yield a statistically significant difference in the incidence of renarcotization. On the other hand, although adequate spontaneous ventilation was always restored during reversal with nalbuphine as well as with naloxone in our study patients, the need to observe for renarcotization to avoid potentially disastrous complications still persists with either drug. In addition, the fact that one of every three patients receiving similar, relatively large doses of fentanyl did not require any opioid antagonism at the end of surgery indicates the enormous variability of the response to opioids and the need to individualize dosage and reversal approaches.

One weakness in this study was that during transport to the recovery room, important hemodynamic alterations may have occurred. Although ideally patients should have had continuous monitoring during the study, we designed the study protocol to adhere to a realistic and acceptable clinical practice. Although a monitoring "blackout" occurred in transport, recovery room measurements, starting immediately after a 2-min transport time, confirm that the two drugs caused similar respiratory and hemodynamic changes.

In summary, either naloxone (0.08 mg) or nalbuphine (2.5 mg) given every 2 min can produce adequate spontaneous ventilation postoperatively after one to four doses in anesthetized patients who re-

Table 6. Patients Requiring Analgesics in the Recovery Room

	Number	Percent
Naloxone	12	40
Nalbuphine	5 ^a	16.7 ^a

^a*P* < 0.05 compared to the naloxone group.**Table 7.** Age Distribution and Number of Patients Developing Systolic Blood Pressure >170 mm Hg After Opioid Antagonism

	Age (yr)		
	<40	>40	>60
Naloxone	4	1	4
Nalbuphine	2	2	1

ceived large doses of fentanyl. Aside from decreasing the need for analgesics in the recovery room, we could find no other significant differences between nalbuphine and naloxone, and both drugs produced similar changes in heart rate, blood pressure, arterial blood gas tensions, respiratory rate, and tidal volume. Although we found both drugs efficacious and safe, the need to observe for and treat renarcotization persists with nalbuphine as with naloxone.

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Effect of Propofol Anesthesia on Baroreflex Activity in Humans

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Previous studies have shown that infusions of propofol, a new intravenous anesthetic, were associated with decreased arterial pressure and slow heart rates. To evaluate the role of baroreflex mechanisms in sustaining these conditions, the effects of two infusion rates of propofol (54 and 108 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) to supplement 66% nitrous oxide in oxygen anesthesia were studied in twelve ASA class I patients having a mean age of 34 years. Baroreflex control of heart rate was studied by perturbing the patients' arterial pressure with phenylephrine or sodium nitroprusside. Valsalva maneuvers were used to assess the response of the systemic

arterial system. Steady state anesthesia at both infusion rates was not associated with decreased sensitivity of the baroreflex control of heart rate, but resetting of the reflex occurred to allow lower arterial pressures for a given heart rate than in the awake state. During propofol infusions at either rate, the diastolic pressure overshoot normally associated with the relief of raised airway pressure in the Valsalva maneuver was significantly reduced. It is concluded that propofol/nitrous oxide anesthesia is not associated with impairment of baroreflex sensitivity, but that central sympatholytic and/or vagotonic mechanisms enable low heart rates to be sustained despite decreased arterial pressures.

Key Words: ANESTHETICS, INTRAVENOUS—propofol. REFLEXES—baroreceptors.

The hemodynamic effects of the intravenous anesthetic 2,6 di-isopropylphenol (propofol, Diprivan) were originally studied using the Cremophor formulation. Induction of anesthesia with this formulation of propofol caused a decrease of systolic and diastolic arterial pressures associated with a 12% decrease in cardiac output and a 9% decrease in systemic vascular resistance (1). The new formulation of propofol as an aqueous emulsion has similar hemodynamic effects, during both induction and maintenance of anesthesia (2-4).

Further information concerning the effects of propofol on the circulation can be obtained by studying its effects on cardiovascular control mechanisms. Arterial baroreceptors are important acute cardiovascular control mechanisms that regulate arterial pressure by modifying systemic vascular resistance, myocardial contractility, and heart rate. Baroreflex control of heart rate has been studied extensively in humans during anesthesia. Both inhalation (5-8) and intravenous anesthetics (5,9,10) have been shown to alter baroreflex activity. This can have important con-

sequences after hemorrhage or postural changes during anesthesia. The purpose of our study was to investigate the effects of continuous infusion anesthesia with propofol on baroreflex activity.

Patients and Methods

Twelve patients aged between 18 and 50 yr (mean 34) undergoing a variety of general surgical procedures were studied. All patients had clinically normal cardiovascular systems. The study was approved by the local Ethics Committee and the Committee on Safety of Medicines, and all patients gave consent after a full explanation of the procedures. Patients received morphine sulfate 0.15 mg/kg IM 1 hr before arrival in the induction room.

Intra-arterial (brachial), central venous (SVC), and peripheral venous cannulae were placed under local analgesia in all patients before induction of anesthesia. The ECG (CM5) and the thoracic impedance wave form were monitored continuously, the latter identifying the onset of the inspiratory and expiratory phases of breathing. Arterial, central venous, and airway pressures were measured with Gould-Statham P231a transducers, amplified by Hewlett-Packard 78205 modules, and recorded on a Siemens-Eléma EM81 ink jet recorder, and on a Racal FM instrumentation tape recorder.

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Table 1. Hemodynamic Variables and Baroreflex Parameters

	Propofol infusion rate			
	Group I (n = 6) 54 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$		Group II (n = 6) 108 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	
	Awake	Anesthetized	Awake	Anesthetized
RR interval (ms)	768 $\pm$ 131	948 $\pm$ 100 ^a	786 $\pm$ 94	970 $\pm$ 165 ^b
Heart rate (beats/min) (range equivalent to $\pm$ SD of RR interval)	78 (67-95)	63 (57-71)	76 (68-87)	62 (53-74)
Systolic arterial pressure (SAP) (mm Hg)	128 $\pm$ 12	89 $\pm$ 10 ^c	130 $\pm$ 12	82 $\pm$ 7 ^c
Diastolic arterial pressure (DAP) (mm Hg)	68 $\pm$ 10	49 $\pm$ 7 ^b	69 $\pm$ 9	49 $\pm$ 8 ^b
Baroreflex slope (Phenylephrine) change in arterial pressure (ms/mm Hg)	10 $\pm$ 5	9 $\pm$ 4 (NS)	9 $\pm$ 3	11 $\pm$ 4 (NS)
RR interval at reference arterial pressure (ms) Phenylephrine	827 $\pm$ 219	1379 $\pm$ 262 ^b	734 $\pm$ 182	1558 $\pm$ 382 ^b
Baroreflex slope Sodium nitroprusside (ms/mm Hg)	7 $\pm$ 5	8 $\pm$ 4 (NS)	4 $\pm$ 1	8 $\pm$ 2 ^b
RR interval at reference arterial pressure Sodium nitroprusside (ms)	791 $\pm$ 190	1233 $\pm$ 371 ^a	743 $\pm$ 129	1461 $\pm$ 253 ^b
Valsalva				
DAP before Valsalva (mm Hg)	64 $\pm$ 12	63 $\pm$ 15	66 $\pm$ 4	50 $\pm$ 6
DAP after Valsalva (mm Hg)	87 $\pm$ 23	69 $\pm$ 12	97 $\pm$ 18	56 $\pm$ 7
Δ DAP (mm Hg)	23 $\pm$ 17	6 $\pm$ 7 (NS)	31 $\pm$ 19	6 $\pm$ 6 ^a

All values $\pm$ SD.

NS = Not significant.

^a $P < 0.05$ by comparison with awake values.^b $P < 0.01$ by comparison with awake values.^c $P < 0.001$ by comparison with awake values.

Anesthesia was induced with propofol 2 mg/kg and maintained with 66% nitrous oxide in oxygen breathed spontaneously through a facemask and Mapleson A system, supplemented immediately by an infusion of propofol at either 54 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (group I) or at 108 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (group II) up to the end of the studies, and throughout the subsequent surgery.

Pressor (phenylephrine), depressor (sodium nitroprusside) tests (12 patients), and a Valsalva maneuver (10 patients) were performed in awake supine patients. These baroreflex function tests were then repeated 30 min after induction of anesthesia before surgical stimulation.

Two components of the overall baroreflex were examined. Baroreflex control of heart rate was assessed by the method of Smyth, Sleight and Pickering (11). The arterial pressure of the subject was transiently increased by a single instantaneous intravenous injection of 75-100 μg phenylephrine, and the reflex decrease of heart rate was detected over the subsequent 30-40 sec by measuring successive RR intervals during the expiratory phase of breathing. With each phenylephrine injection the regression of RR interval against the preceding systolic arterial pressure (SAP) was calculated (5). The slope of this linear relation is

a measure of baroreflex sensitivity and is expressed in msec of RR interval change per mm Hg change in SAP. A similar relation was determined for the increase in heart rate induced in response to a decrease of arterial pressure after a single instantaneous IV injection of 50 μg sodium nitroprusside. From the same regression analyses the RR interval at the reference arterial pressure was derived as a measure of reflex resetting (5).

Baroreflex control of arteriolar constriction was assessed by measuring the overshoot in diastolic arterial pressure during the recovery phase of the cardiovascular response to the Valsalva maneuver. The overshoot during this phase is associated with the increase in blood pressure above the level at rest caused by the return of cardiac output after release of the raised airway pressure, coupled with an increased systemic vascular resistance reflecting the continuing baroreceptor reflex arteriolar constriction (12,13). Patients were trained to perform Valsalva maneuvers using a mask connected to an aneroid manometer, raising airway pressure to 25-30 mm Hg and sustaining this pressure for 15 sec while recording HR and BP changes. The difference was calculated between the rest diastolic pressure before the Valsalva maneuver and the

peak overshoot during the recovery phase. During anesthesia, Valsalva maneuvers were performed by sustained manual lung inflation to the same pressure, and for the same duration, as that achieved by the conscious patient.

Statistical evaluation of the results within groups was based on paired two-tailed Student's *t*-test with correction for the Bonferroni inequality of variances. Comparisons between groups I and II were analyzed by unpaired Student's *t*-test.

Results

There were no significant differences between the values of arterial pressure and heart rate in the two groups of patients before anesthesia, nor in the mean values for the derived parameters of baroreflex control (Table 1).

Group I

Thirty minutes after induction, during infusion of propofol at $54 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, systolic and diastolic arterial pressures decreased by 30 and 28% respectively ($P < 0.001$), and heart rate decreased by 23% ($P < 0.05$). In response to a phenylephrine challenge, there was no significant change in the slope of the RR interval/SAP relation when compared with the awake value (Fig. 1), but there was significant resetting as reflected in the RR interval at reference arterial pressure ($P < 0.01$). The mean value for the slope of the RR interval/SAP relation in response to the sodium nitroprusside challenge in the awake patients was lower than that induced by phenylephrine (NS). There was no significant change in this slope during propofol anesthesia, but there was significant resetting of the reflex ($P < 0.01$) to allow a slower heart rate at a lower rest arterial pressure. In response to the Valsalva maneuver there was a mean diastolic pressure overshoot of 23 mm Hg in the awake patients, but only 6 mm Hg during propofol infusion (NS).

Group II

During infusion of propofol at $108 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ the phenylephrine-induced baroreflex slope was not significantly different from that in the awake patients. However, the sodium nitroprusside-induced baroreflex slope was double ($P < 0.01$) that in the awake patient. Both phenylephrine ($P < 0.05$) and sodium nitroprusside ($P < 0.01$) challenges showed marked resetting of the baroreflex, allowing slower heart rates at the lower arterial pressures during anesthesia. There

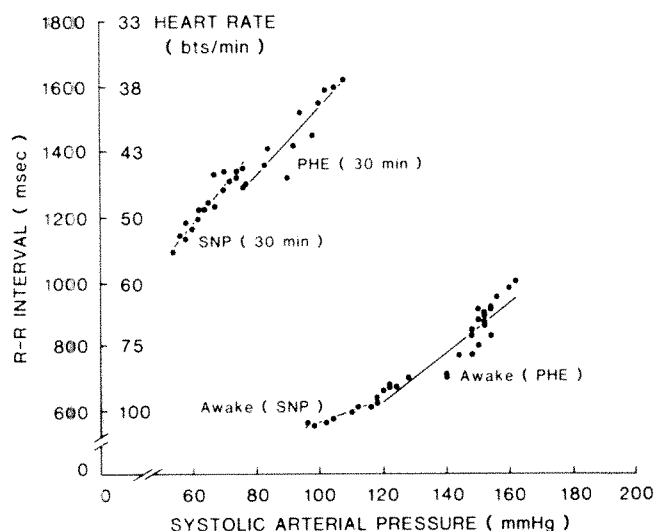


Figure 1. Relation between R-R interval (and heart rate) and systolic arterial pressure in one patient illustrating the responses to pressor (PHE) and depressor (SNP) perturbations of arterial pressure in the awake patient (right), and during infusion of propofol ($108 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) during nitrous oxide anesthesia (left). The responses during propofol anesthesia show marked reflex resetting in that the baseline arterial pressures before perturbation (upper end of SNP response, lower end of PHE response) are markedly lower than in the awake patient, although the baseline heart rate is slow (about 53 beats/min).

was a mean diastolic pressure overshoot of 31 mm Hg after the Valsalva maneuver in the awake patients, but this was reduced to 6 mm Hg ($P < 0.05$) during propofol infusion.

Discussion

This study has shown that during nitrous oxide anesthesia, in the absence of surgery, baroreflex control of heart rate was not significantly depressed by either infusion rate of the new intravenous anesthetic propofol. This is in direct contrast with the findings of previous studies of intravenous or inhalation anesthetics with the possible exception of methoxyflurane (14). Pressor slopes (phenylephrine) in the awake patients were steeper than the depressor (sodium nitroprusside) slopes. This may be because an increase in cardiac sympathetic tone produced by lowering blood pressure elicits smaller changes in heart rate relative to the increase in parasympathetic activity produced by raising arterial pressure (8). In our study, depressor slopes increased during propofol infusion at $108 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, but not at the lower infusion rate. This could reflect increased sympathetic nervous responsiveness to a further decrease of arterial pressure induced by the sodium nitroprusside. Comparable

studies have not been performed during infusions of other intravenous anesthetics.

Bristow et al. (5), using a similar quantitative method of baroreflex function testing, found that halothane 0.5–1% in conjunction with nitrous oxide significantly depressed baroreflex function. Subsequently, Duke et al. (6) also demonstrated that 1.25 MAC halothane or enflurane nearly abolished baroreflex sensitivity. More recently, Kotrly et al. (8) showed a 30% depression of baroreflex activity with 1.0 MAC isoflurane and a 58% depression with 1.5 MAC isoflurane.

Similar degrees of depression of baroreflex sensitivity have been demonstrated within a few minutes of injecting IV anesthetic agents. Shortly after induction with thiopental (5), Althesin (9), or methohexital (10), baroreflex sensitivity for control of heart rate has been shown to be markedly depressed with resetting of the set point in such a way as to allow a *faster* heart rate (shorter RR interval) at the *lower* arterial pressure. This increased heart rate after induction of anesthesia is often interpreted as a baroreflex response to the decrease of arterial pressure, but this has not been supported by the finding of a marked decrease of baroreflex sensitivity (5,9,10). Thus one can ascribe this state of reflex resetting to either increased central sympathetic activity or decreased central parasympathetic activity, or both. As plasma catecholamine concentrations have been consistently found to be reduced within a few minutes of induction of anesthesia (15,16), and animal studies have shown decreased cervical sympathetic nerve activity (17), the hypothesis of increased sympathetic nervous activity is difficult to sustain. Therefore, one can postulate that a mechanism involving decreased central parasympathetic activity is responsible.

During maintenance of anesthesia with either volatile or gaseous anesthetics (5), or with Althesin infusions (9), the set point of the reflex is reset to allow a *slower* heart rate (greater RR interval) despite the *decreased* arterial pressure. As baroreflex sensitivity has always been shown to be depressed under these conditions, one must presume that this state is maintained by a central vagotonic, or sympatholytic mechanism, or both.

Methohexital was shown to be different (10) in that during continuous infusion, both *before* and during surgery, the heart rate was *increased* at a lower arterial pressure despite marked (50–60%) depression of baroreflex sensitivity. Skovsted, Price, and Price (17) found that thiopental and methohexital caused a marked decrease in cervical sympathetic nervous activity in cats, which was enhanced in baroreceptor-denervated animals, but showed that barostatic reflex responses to aortic depressor nerve stimulation were

diminished but not abolished. Unfortunately, it is difficult to compare their results with those of Carter et al. (10), because Skovsted paralyzed his animals with gallamine, a muscle relaxant known to exert peripheral vagolytic responses. Thus we would propose that a sustained central inhibition of vagal (parasympathetic) activity could account for the findings during methohexital anesthesia.

Propofol infusion, at both 54 and 108 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, was associated with resetting of the reflex set point to allow slower heart rates (increased RR interval at reference arterial pressure) despite decreased arterial pressures (Table 1). In this respect propofol resembles Althesin given by continuous infusion, or the common gaseous and volatile anesthetics, and may be regarded as exerting a central vagotonic (and/or sympatholytic) effect. This finding should alert the anesthesiologist to the possibility that the combination of propofol infusion with other centrally vagotonic drugs, such as fentanyl and its congeners, may result in slower heart rates than with propofol infusions alone.

Our measurements of baroreflex function during propofol infusion were done approximately 30 min after commencing an infusion of propofol (after a single loading dose). Previous studies using the same infusion strategy (18) have shown that the whole-blood concentrations of propofol achieved at that time were approximately 90–95% of the values achieved during subsequent sustained infusions (3). We did not consider the further delay of the start of surgery for the purposes of establishing a near-steady state to be justifiable.

The striking difference observed in the present study was the lack of depression of baroreflex sensitivity compared with our studies of other intravenous and inhalational anesthetics. This could be regarded as an advantage in that the chronotropic response to hemorrhage would not be blunted as it is with many other anesthetics.

A second aspect of baroreflex cardiovascular control, namely regulation of arteriolar constriction, was also explored in the present study and was found to be markedly attenuated during propofol/nitrous oxide anesthesia. The assessment of baroreflex regulation of arteriolar tone is difficult for two reasons. First, the onset and time course of the systemic arteriolar constriction, mediated by activation of sympathetic nerve activity, is slow (19). Second, there is no convenient direct beat-by-beat measurement that can be compared, for instance, with heart rate (RR interval).

The hemodynamic response to a Valsalva maneuver in an awake subject, or to an equivalent increase in airway pressure induced by sustained lung inflation in the anesthetized patient, allows certain obser-



vations to be made with respect to baroreflex control. The normal reflex increase of heart rate in response to the decrease of arterial pressure during sustained lung inflation (Valsalva maneuver) is another means of confirming the baroreflex control of heart rate. The overshoot of diastolic arterial pressure after release of sustained lung inflation is regarded as an indication of baroreflex-induced systemic arteriolar constriction, and has been used as a means of quantifying changes associated with autonomic neurologic control (12,13). It has also been used as a means of investigating the reflex cardiovascular responses to gaseous or volatile anesthetics (20,21).

In the present study we observed a consistent and significant decrease of the diastolic overshoot after a Valsalva maneuver (or equivalent sustained lung inflation) during propofol infusion anesthesia, the effect being more marked in patients receiving the higher infusion rate. However, this may simply reflect a direct target organ depression by the anesthetic; that is, propofol may cause a direct impairment of vascular smooth muscle activity. Most commonly used inhalation, and to a lesser extent intravenous, anesthetics cause significant direct myocardial depression by effects on calcium flux and/or calcium binding. Concentrations of anesthetics used to induce surgical anesthesia exert direct depressant and vasodilator effects on vascular smooth muscle coupled to their depression of sympathetic outflow. This could in part explain the decreased baroreflex control of systemic vascular resistance demonstrated in the present study. Further studies are clearly necessary to elucidate this mechanism.

The pressure of arterial carbon dioxide was not monitored during this study. It is unlikely that changes in PaCO_2 would have much influence on the sensitivity or resetting of the baroreflex. Hypercapnia alone has been shown to have little effect on baroreflex sensitivity, and to cause a minor degree of resetting in the direction opposite to the effects of anesthesia (22).

Conclusions

Pharmacologic and mechanical manipulations of blood pressure measure overall baroreflex activity in terms of response, e.g. heart rate or diastolic overshoot. On the basis of such information, one cannot define where the locus or loci of altered activity may be. Possible sites include baroreceptors, afferent pathways, integrating centers in the nervous system, efferent sympathetic or vagal pathways, or effector organs. Halothane has been shown to increase the frequency of discharges in single fibers of the carotid sinus nerve at any given pressure (23,24). This apparent sensi-

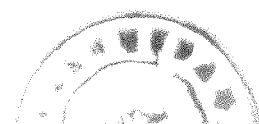
tization of receptors could in part explain the marked resetting of the reflex observed during anesthesia with halothane, Althesin, or propofol. Anesthetic agents have also been found to depress central nervous system centers that regulate reflex activity of the cardiovascular system. Skovsted and Price (25) showed that halothane inhibited the 'pressor' (sympathetic) medullary outflow without substantially inhibiting the 'depressor' (parasympathetic) outflow thus allowing a decrease in blood pressure and slower heart rate than in the resting state. Isoflurane, thiopental, and methohexital differ from other anesthetics in that their administration is associated with a tachycardia coupled with a decrease of blood pressure, which is due in part to a greater inhibition of central parasympathetic activity than the sympathetic nervous system. This could be construed as an indication of baroreflex activity leading to increased sympathetic outflow were it not for the almost complete suppression of the heart rate response to a pressor stimulus.

Propofol infused during nitrous oxide anesthesia presents different effects on baroreflex control mechanisms than do other anesthetics. It appears to allow marked resetting of the reflex set point without depressing baroreflex sensitivity. This implies that the mechanisms responsible for enhanced parasympathetic control of heart rate are much stronger than the baroreflex mediated enhancement of central sympathetic activity.

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The Effects of Bupivacaine on the Umbilical Circulation and Placental Gas Exchange in the Fetal Lamb

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FLEMING JA, LAMBERT TF, WALKER AM. The effects of bupivacaine on the umbilical circulation and placental gas in the fetal lamb. *Anesth Analg* 1987;66:1121-6.

Seven chronically catheterized fetal sheep at 125-140 days gestation were studied in 12 experiments to determine the direct effects of the local anesthetic bupivacaine (infused intravenously to the fetus) on the umbilical circulation and placental gas exchange. Electrocardiac activity, umbilical blood flow, heart rate, and umbilical arterial and venous pressures were continuously monitored in experiments comprising a baseline period, a drug infusion period and a recovery period, each of 2 hr duration. Samples of umbilical arterial and venous blood were taken for blood gas analysis, and for bupivacaine assay using high pressure liquid chromatography technique. Fetal plasma bupivacaine levels were $1.3 \pm 0.3 \mu\text{g/ml}$ (mean $\pm$ SEM) between 60-120 min of infusion. Heart rate and umbilical blood flow decreased significantly to 89 and 94% of control, respectively, ($P < 0.05$) during the infusion and returned to control levels by 2 hr afterwards. Mean umbilical arterial and venous pressures were not significantly altered, and no significant rise in umbilical vascular resistance occurred. No changes occurred in umbilical arterial or venous pH, PO_2 , or PCO_2 . In summary, bupivacaine reversibly depressed fetal heart rate and umbilical blood flow without detrimental changes in fetal blood gas or acid-base status.

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Key Words: ANESTHETICS, LOCAL—bupivacaine. ANESTHESIA—obstetric.

Cardiovascular problems have been associated with the use of the local anesthetic bupivacaine in adults (1-6), and there is considerable interest and uncertainty about the potential toxicity of bupivacaine on the fetal cardiovascular system after routine epidural administration for labor or cesarean section. Bupivacaine has been regarded widely as a suitable and safe agent for epidural analgesia during labor, because the fetal to maternal total plasma concentration ratio of bupivacaine is low (0.2-0.4) when compared with other local anesthetics (7). However, the pharmacologically active, unbound fraction in fetal plasma is comparatively high, because fetal plasma proteins bind bupivacaine to a lesser extent than do maternal plasma proteins; moreover the drug is highly lipid soluble and there is no transplacental barrier to the

unbound fraction (8). Recent evidence that bupivacaine and its metabolites may be detected in neonatal blood for 3 days postpartum (9) supports the view that there is significant fetal tissue accumulation of the local anesthetic during the course of epidural analgesia. Tissue accumulation may be even greater in the acidotic fetus by way of ion-trapping across the placenta (10-13). Suspicions of fetal cardiovascular toxicity have been raised by fetal heart rate abnormality during labor (14,15) and by in vitro studies of isolated fetal vessels (16,17), but there are limited data available that directly address the question of fetal toxicity.

This study examined whether bupivacaine in fetal plasma impaired the umbilical circulation and placental gas exchange. Bupivacaine was administered directly to fetal sheep in utero to circumvent maternal cardiovascular effects of local anesthesia. Infusion rates were selected to avoid neurologic toxicity and to approach the plasma bupivacaine concentrations measured in cord blood after epidural anesthesia. The study correlated umbilical blood flow, fetal blood pressure, heart rate, electrocardiac activity, and blood gases and pH with assayed drug levels in umbilical arterial plasma.

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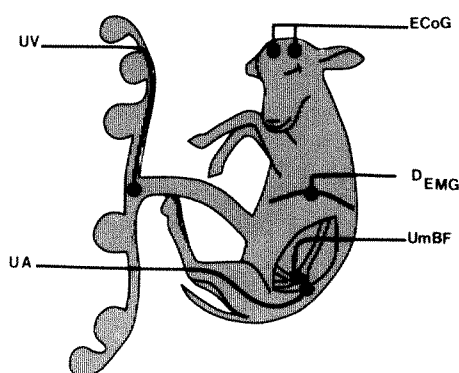


Figure 1. Schematic illustration of the chronically instrumented fetal lamb. ECoG, electrocorticogram electrodes. EMG, diaphragm electromyogram electrode. UmBF, umbilical blood flow transducer. UA, umbilical arterial catheter. UV, umbilical venous catheter.

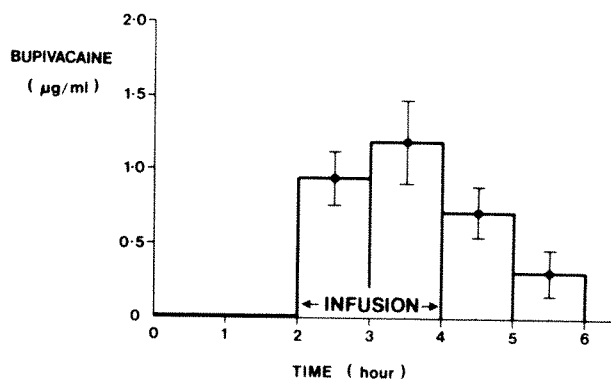


Figure 2. Plasma bupivacaine concentrations before, during, and after the bupivacaine infusion to the fetus. Values are mean $\pm$ SEM, for 12 studies in seven fetal lambs.

Material and Methods

Animal Preparation and Measurements

Chronically instrumented fetal lambs (Fig. 1) were surgically prepared and studied after full recovery from the stresses of surgery and anesthesia. Seven fetal lambs of accurately known gestation were used. Pregnant ewes (Border Leicester-Merino cross) at 110 days gestation (term is 147 days) were anesthetized with thiopentone (Pentothal, Abbott 5% w/v) and, after intubation, by a halothane (1-2%) -oxygen mixture. With the ewe supine, the fetus was partially exteriorized via incisions in the abdominal wall and gravid uterine horn and kept warm and moist with warm saline-soaked towels.

Bipolar silver electrodes to measure electrocortical activity (Neotrace amplifier-filter NT114-NL 125) were positioned onto the parietal dura through small holes drilled in the skull, 1 cm either side of the sagittal suture, and firmly fixed with dental acrylic.

A cuff-type electromagnetic flow transducer 5-7 mm in diameter (C. and C. Instruments) was placed around the common umbilical artery for measurement of pulsatile and mean umbilical blood flows (Micron RC 1000) (18).

Intravascular polyvinyl catheters were positioned at the origin of the common umbilical artery (retrogradely via a pedal artery) and in the umbilical vein (via a placental cotyledonary vein). Catheter positions were determined by prior measurements and were checked at the completion of the study. These allowed direct measurement of umbilical arterial and venous pressures, and enabled sampling of blood for hemoglobin oxygen saturation (Radiometer OSM2), blood gas and pH analysis (Corning 168), and bupivacaine assay (noted later). A third intravascular catheter was

passed into the fetal inferior vena cava via a pedal vein for infusion of bupivacaine.

A catheter fixed to the fetal thorax at the level of the heart served as a zero-reference for fetal intravascular pressures. The fetus was then gently replaced and the uterus closed. Catheters were filled with heparin-saline solution (1000 heparin units/ml) and, together with the other leads, exteriorized through the flank of the ewe, and the abdomen was closed in layers. The animals were given antibiotic, 250 mg of dihydrostreptomycin sulphate and 250 mg of procaine penicillin (Streptopen, Glaxovet), followed by weekly injections of 235 mg benethamine penicillin, 125 mg procaine penicillin, and 150 mg benzylpenicillin (Triptopen, Glaxovet) thereafter. Fifteen days were allowed for full recovery from surgery before this study commenced. After the study the maternal ewes were killed, the fetal weight was determined, and the correct positioning of catheters and flow transducer was checked.

Recordings

One hour before a recording session, the ewe was moved into a cage in a quiet laboratory. Fetal physiological parameters were recorded using a multi-channel chart recorder (Hewlett-Packard 7758A). Selected measurements (including electrocortical activity) were also recorded on a four-channel electromagnetic tape recorder (Tandberg series 100) for later analysis.

Each 6-hr recording session was divided into three consecutive periods of 2 hr: a control period, a period during which bupivacaine was continuously infused (Sage Instruments 341A or Harvard 901A) at approximately $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and a recovery period.

Table 1. Fetal Cardiovascular Measurements Before, During, and After Bupivacaine Infusion

	Number of experiments	Control	Bupivacaine	Recovery
Heart rate (beats/min)	12	178 ± 4	158 ± 2 ^a	182 ± 3
Umbilical flow (ml·kg ⁻¹ ·min ⁻¹)	9	199 ± 20	187 ± 20 ^b	191 ± 20
Blood pressure (mm Hg)				
Umbilical artery	10	49 ± 1	50 ± 1	48 ± 1
Umbilical vein	5	8 ± 1	8 ± 1	6 ± 1
Umbilical vascular resistance [mm Hg/(ml·kg ⁻¹ ·min ⁻¹)]	5	0.21 ± 0.03	0.24 ± 0.04	0.22 ± 0.03

Values are mean ± SEM.

^a*P* < 0.001.^b*P* < 0.05.

Drug infusion rates were initially estimated using a standard curve relating fetal weight to gestational age based on 140 measurements made in this laboratory, and recalculated when fetal weight was measured after the study. The total volume infused did not exceed 5% of estimated fetal blood volume.

Umbilical arterial blood samples (1.5 ml), collected at half-hour intervals throughout the drug infusion and recovery period, were centrifuged and the plasma frozen for determination of plasma bupivacaine concentration using a high pressure liquid chromatography (HPLC) technique (19). Prepared plasma extracts were injected into a du Pont 25-ODS Zorbax HPLC column, and analyses performed on a Perkin Elmer Series 2 chromatograph and LC spectrophotometer set at 205 nm wavelength. Bupivacaine concentrations were calculated from computed peak areas (LDC model 304 Computing Integrator) using lignocaine as an internal standard, and values were averaged for each hour of the drug infusion and recovery periods. At the end of each 2-hr period umbilical arterial and venous blood samples (0.2 ml) were taken for blood gas and pH analysis at 39°C.

Data Analysis

Cardiovascular data were read from each record at 5-min intervals and averaged for the control period, and read at the second hour of each of the drug infusion and recovery periods. We calculated umbilical vascular resistance (umbilical artery – umbilical vein) as pressure divided by umbilical flow. All data were expressed as mean ± SEM, and significance of differences was evaluated using Student's *t*-test (*n* = 8.12) or Wilcoxon signed-ranks test (*n* = 5) for paired data, with *P* < 0.05 (two-tailed test) considered significant.

Results

Twelve studies were conducted between 125–140 days of gestation. With one exception, animals were in

good health throughout our study, as judged by normal cardiovascular, blood gas, and pH measurements.

Plasma Bupivacaine Concentrations

Plasma bupivacaine levels measured in 12 studies (Fig. 2) peaked at 1.3 ± 0.3 μg/ml during the second hour of infusion, and decreased toward baseline levels during the recovery period. Plasma bupivacaine remained elevated (0.3 ± 0.2 μg/ml) in the second hour of recovery, and in many animals local anesthetic was still detectable two hours after cessation of infusion.

Peak concentrations in individual fetuses were spread over a wide range (0.2–3.2 μg/ml); these correlated poorly with the calculated infusion rates, which varied over a comparatively narrow range (0.07–0.19 mg·kg⁻¹·min⁻¹). The highest concentration was obtained in a fetus which was spontaneously growth retarded (body weight 70% of normal) and relatively hypoxemic (PO₂ 25 mm Hg and 7 mm Hg in umbilical vein and artery, respectively), though not acidemic.

Cardiovascular Data

Bupivacaine infusion resulted in a significant depression of average fetal heart rate to 89 ± 1% of control during the second hour of the infusion period (Table 1) (*P* < 0.05). Heart rate and blood flow subsequently returned to baseline over the 2-hr recovery period. No significant changes occurred in umbilical arterial or venous pressures. Heart rate and umbilical flow in the spontaneously hypoxemic fetus changed by +4% and –6%, respectively. Umbilical vascular resistance increased during bupivacaine infusion in four of five experiments, but overall the change did not achieve statistical significance.

Blood Gas and Acid-Base Status

Control blood gas and acid-base measurements taken from both umbilical vein and artery spanned the nor-

Table 2. Fetal Blood Gas and Acid-Base Measurements Before, During, and After Bupivacaine Infusion

	Number of experiments	Control	Bupivacaine	Recovery
Umbilical Vein				
PO ₂ (mm Hg)	8	30 ± 2	29 ± 3	30 ± 4
SO ₂ (%)	10	77 ± 4	75 ± 3	76 ± 3
PO ₂ (mm Hg)	8	45 ± 2	46 ± 1	46 ± 1
pH	8	7.40 ± 0.01	7.39 ± 0.01	7.41 ± 0.00
Base excess (mM/L)	8	3.8 ± 0.6	3.3 ± 0.6	4.6 ± 0.4
Umbilical Artery				
PO ₂ (mm Hg)	10	17 ± 1	16 ± 2	17 ± 2
SO ₂ (%)	12	44 ± 3	39 ± 4	39 ± 4
PCO ₂ (mm Hg)	10	52 ± 2	53 ± 2	53 ± 1
pH	10	7.35 ± 0.01	7.35 ± 0.01	7.35 ± 0.01
Base excess (mM/L)	10	2.9 ± 0.8	3.1 ± 0.7	3.6 ± 0.7

Values are mean ± SEM.

mal range for fetal preparations of this kind. As noted earlier, one fetus was spontaneously hypoxemic but not acidemic. Average values for the entire study group are shown in Table 2. Irrespective of control values, there was no alteration in the blood gas or pH status of any animal during or after the bupivacaine infusion.

Electrocortical Activity

The electrocorticogram (ECOG) revealed no overt neurologic toxicity in any animal during the recording period. All animals continued to cycle normally between rapid eye movement sleep (low voltage ECOG) and quiet sleep (high voltage ECOG) with no significant difference in time spent in either sleep state. Epoch lengths for low voltage and high voltage ECOG averaged 13 ± 2 and 10 ± 1 min in the control period, 14 ± 2 and 12 ± 2 min during bupivacaine infusion, and 15 ± 2 and 14 ± 1 min in the recovery period, respectively.

Discussion

In this study, peak plasma bupivacaine concentrations ranged from 0.24 to 3.1 µg/ml in the fetal lamb umbilical arterial circulation. In human neonates, after uncomplicated maternal epidural anesthesia, plasma bupivacaine concentrations averaged 0.14 µg/ml, with the maximum value being 0.48 µg/ml (20). However, more information relating to fetal plasma protein binding of this drug is required before the free (effective) concentrations can be strictly compared in lambs and neonates. Recent estimates (21) of adult plasma protein binding of bupivacaine suggest that this is slightly higher in sheep (98%) than in human (96%) plasma, resulting in lower effective concentrations of

free drug at an equivalent total plasma concentration in sheep. If a similar difference exists for fetal blood, we could expect that the slightly greater plasma concentrations obtained in the present study would result in free drug concentrations that are comparable with clinically obtained levels.

Although we obtained comparable levels of bupivacaine concentration during the infusion period in this model, the pharmacokinetics of the drug differ markedly from the clinical situation. During epidural anesthesia in labor, bupivacaine is administered to the mother, and local anesthetic flow across the placenta is from mother to fetus until equilibrium occurs. On delivery the neonate is responsible for metabolism and excretion of bupivacaine and its byproducts, which may be detected in its tissues for several days (9). In this model, maternal tissues act as a large reservoir for the local anesthetic administered to the fetus, buffering acute increases in bupivacaine concentration during the infusion period and allowing rapid elimination of bupivacaine from fetal tissues during the recovery period. Placental function will have a major role in determining fetal plasma bupivacaine concentration and its rate of decline.

We found a wide range of bupivacaine concentrations despite similar infusion rates to the fetus. Plasma concentration correlated poorly with infusion rate; the highest level was found in a fetus that was spontaneously hypoxemic and growth retarded. The higher levels of bupivacaine probably reflect diminished placental function and a lower rate of transfer to the maternal circulation in these experiments.

This study demonstrated that bupivacaine, at plasma concentrations comparable to those obtained after routine epidural anesthesia, has small but significant cardiovascular effects in the fetal lamb, characterized by concurrent reversible depression of heart rate and

umbilical blood flow. These effects were also minimal in a case of spontaneous hypoxemia, in association with high plasma concentrations of the drug. Whether both effects were related to direct local anesthetic toxicity or whether one occurred consequent to the other is open to question.

Bradycardia, hypoxia, and acidosis have been reported (22-25) after the use of local anesthetic amides for paracervical blockade. As both the uteroplacental circulation and the fetus were exposed to high drug concentrations, the site of primary toxicity could include the myometrium, the uterine circulation, the umbilical circulation, or the fetal myocardium. The uterine vasculature is certainly implicated, as in vitro studies of strips of uterine artery have shown a direct vasoconstrictor effect of many local anesthetics including bupivacaine (22). Local anesthetics can directly depress the isolated fetal myocardium, particularly in the acidotic state (26). Moreover, bupivacaine used in routine epidural anesthesia in healthy parturients may affect fetal hemodynamics. In contrast to 2-chloroprocaine, bupivacaine epidural anesthesia increased fetal heart rate variability (14) and precipitated transient abnormalities of fetal heart rate, notably late deceleration patterns (15).

Both animal and in vitro studies have pointed to the umbilical circulation as a site of vascular toxicity, but this is not clearly established. Morishima et al. (27) demonstrated reduced umbilical blood flow in acidotic fetal sheep after lidocaine was infused intravenously into the mother. However, they were unable to define to their satisfaction whether the reduced flow was due to a direct toxic effect of lidocaine on the umbilical circulation, or was secondary to fetal hypoxia and bradycardia after altered maternal hemodynamic state or uterine bloodflow changes. Two independent studies (16,17) of isolated strips of human umbilical artery showed that bupivacaine may cause umbilical vasoconstriction. It was postulated that epidural anesthesia might diminish umbilical blood flow through umbilical vasoconstriction and compromise placental gas exchange, resulting in fetal hypoxemia, bradycardia, and arrhythmia. However, our findings do not support this hypothesis. We were not able to demonstrate a significant increase in umbilical vascular resistance, a major decrease of umbilical flow, nor any change in blood gas or acid-base status during the infusion.

Umbilical flow decreased slightly without a demonstrable increase in umbilical vascular resistance or decrease in umbilical arterial pressure, but in association with a concomitant bradycardia. This may reflect the strong direct relation between fetal heart rate and umbilical flow noted by Berman et al., (28).

These authors (28) have proposed that umbilical vascular impedance increases as heart rate decreases, independent of caliber changes of placental resistance vessels. This explanation has been challenged (29). Our data might reflect the existence of a heart rate-umbilical blood flow relation. Alternatively, we cannot exclude the possibility that increasing umbilical vascular resistance may have contributed to the decreased flow. Vascular resistance measurements were limited to five experiments because of technical difficulties in accurate long-term umbilical venous pressure measurement. Vascular resistance increased in four of five experiments, without reaching significance. Further study is needed to distinguish between these alternative mechanisms of flow reduction during bupivacaine infusion.

In summary, we propose that bupivacaine, in the plasma concentration range $1.3 \pm 0.3 \mu\text{g/ml}$, had no detrimental effects on fetal well-being, as reflected by undisturbed blood gas and acid-base status. However, bupivacaine significantly depressed fetal heart rate. The question remains as to whether this depression relates to a direct effect of bupivacaine on the fetal myocardium, or is mediated neurologically. There was also a small reversible effect on umbilical blood flow, which may be explained by the concomitant bradycardia or by a minor increase in umbilical vascular resistance. Further investigation of the effects of bupivacaine on the fetal myocardium and vasculature are warranted.

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Venous Air Embolism and Active Lung Inflation at High and Low CVP:

A Study in "Upright" Anesthetized Sheep

John Pfitzner, FFARCS, and Alan G. McLean, FFARCS

PFITZNER J, McLEAN, AG. Venous air embolism and active lung inflation at high and low CVP: A study in "upright" anesthetized sheep. *Anesth Analg* 1987;66:1127-34.

To assess the safety and efficacy of the maneuver of active lung inflation (ALI) after venous air embolism, measurements were made of pulmonary artery occlusion pressure (PAOP), central venous pressure (CVP), and superior jugular bulb pressure (JbP) as an index of cerebral venous sinus pressure in eight sheep before and after a 2-ml/kg air embolus

and before and in the release phase of an ALI to a pressure of 4 kPa (30 mm Hg). (PAOP-CVP) difference decreased significantly after the air embolus with a further decrease after ALI ($P < 0.01$). An increase in JbP occurred with ALI only when the CVP was elevated before the injection of air. After air embolism in neurosurgery, ALI may increase the likelihood of paradoxical embolism in patients at risk and may also fail to help in identifying the site of air entry.

Key Words: EMBOLISM—air. NEUROSURGERY—sitting position.

During neurosurgery in the sitting position, controlled neck compression with an inflatable neck tourniquet (1) has been recommended to facilitate identification of a patent vein in the operative field and also to prevent, promptly and efficiently, further venous air embolism. An alternative maneuver is to apply a positive pressure to the lungs (2-5), using either positive end-expiratory pressure (PEEP) or active lung inflation (ALI) with manual compression of an anesthetic reservoir bag.

Some doubt exists, however, about both the safety and the efficacy of this latter maneuver after venous air embolism. It has been shown that the application of increased airway pressure may result in right atrial pressure becoming greater than the left atrial pressure and therefore in a predisposition to paradoxical embolism in patients at risk (6-9). In fact paradoxical air embolism has been reported in a patient given repeated Valsalva maneuvers in the course of neurosurgery in the sitting position (10).

As regards efficacy, it would appear that although the maneuver may be effective in increasing cerebral venous pressure to above atmospheric levels in at

least some clinical situations (2-5), it has not proved reliable in any of the previously described animal models (1,11,12).

The present studies in upright anesthetized sheep after sudden, large air emboli (2 ml/kg injected over 30 sec) were undertaken with two aims. The first aim was to explain why, in the clinical situation, the use of ALI after air embolism has been reported to have resulted in the escape of air bubbles and blood from an open vein (2-4), whereas in animal models PEEP has not increased cerebral venous pressure (1,11,12). The second aim was to assess whether ALI to pressures of 4 kPa (30 mm Hg) might not further aggravate the already existing risk in upright, anesthetized patients (13) of the right atrial pressure becoming higher than the left atrial pressure.

Because air injected into a peripheral vein can be delayed in its passage to the heart (14-19), and because collections of air in a vertically placed superior vena cava (SVC) will transmit venous pressure upward without the expected falloff in hydrostatic pressure (19) each of the present studies was carried out before and after elevation of the central venous pressure (CVP) with an infusion of 20 ml/kg Dextran 70. Furthermore, to assess the effect of repeated air embolism, each study was repeated 15 min after the previous one, although this part of the protocol was abandoned when animal 4 died after the first repeated embolus.

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Methods

Nine fasting sheep (one of which died during the second part of the study) weighing 32.7 ± 2.6 kg were anesthetized with 25 mg/kg pentobarbital and ventilated with 100% oxygen and 1–2% halothane at a constant tidal volume using a Manley ventilator. The tidal volume and fresh gas flow-rate were set to give a respiratory rate of 12 breaths/min and an end-tidal CO_2 concentration of between 4 and 4.5%. The sheep were positioned "upright," with the hindlegs tucked under the body, the forelegs outstretched, the chest tilted 40° head up, the neck erect, and the head facing forward.

Before positioning the sheep, catheters for monitoring pressures were inserted in the main artery of the foreleg, the superior vena cava or right atrium after withdrawal from the right ventricle, the main pulmonary artery, a peripheral pulmonary artery, and the superior jugular bulb to provide an index of cerebral venous sinus pressure. The main pulmonary artery catheter was passed 3 cm beyond the pulmonary valve and the peripheral pulmonary artery catheter was floated to where occlusion pressures could be recorded; both catheters were 5F-gauge catheters with 0.8-ml balloons. The jugular bulb catheter (1) was inserted into the great vein of the neck and threaded cranially to a point beyond which further advancement resulted in line obstruction.

A four-channel recorder (Elcomatic EM 740) was used to record CVP, PAOP, systemic arterial pressure, and pulmonary artery pressure alternately via a two-way stopcock to a third transducer, and jugular bulb pressure (JbP) and airway pressure alternately also via a two-way stopcock. Of the four transducers (Elcomatic EM 750), the three used to measure CVP, PAOP, and alternately systemic arterial pressure and pulmonary artery pressure were set at right atrial level, while the fourth transducer to measure alternately JbP and airway pressure was set at the level of the tip of the cannula in the jugular bulb. Intraflo continuous flushing devices were used on each of the vascular pressure lines.

Air emboli (2 ml/kg) were injected over 30 sec into a cannula inserted in a cranial direction into the great vein of the neck on the same side as the jugular bulb cannula. The air injections were made, first, with the animal normovolemic and, second, after the administration over 30 to 45 min of 20 ml/kg Dextran 70. In sheep 1, 2, and 3, both emboli were repeated after a period of 15 min, but this part of the protocol was abandoned when sheep 4 died after the first repeat.

Active lung inflation (ALI) was performed, in a standard manner, both before and 30 sec after completion of the injection of each air embolus. Using

manual compression of the anesthetic reservoir bag, the airway pressure was increased from 0 to 2 kPa over 5 sec, maintained steady at 2 kPa for 5 sec, and then increased to 4 kPa over a further 5 sec before being released. Because six pressure recordings were being made on a four-channel recorder, each ALI was performed twice, first while recording CVP, PAOP, pulmonary artery pressure, and JbP and then approximately 12 ventilator breaths later while recording CVP, PAOP, systemic arterial pressure, and airway pressure (Fig. 1).

When ALI after an air embolus resulted in a recorded increase in JbP, the lung inflation sequence was repeated every 2 to 3 min until these peaks of JbP no longer occurred (Fig. 1).

It is proposed that the peaks of JbP were dependent on upward transmission of venous pressure through temporary collections of air in the SVC and neck veins. These collections might occur as continuous columns or as separate pockets of air. The "effective height" of an air collection, defined as that vertical height of air that would be required in an upright distended venous system to result in a particular peak in JbP from a particular peak in CVP, has been calculated using a formula derived schematically from Figure 2. When as a consequence of a venous air collection ALI generates a peak of pressure at superior jugular bulb level, the peak pressure throughout the length of the continuous air collection will be equal to the peak JbP. Because the peak pressure in the SVC or the neck vein at the lower margin of the air collection will be equal to the peak JbP, the peak pressure at right atrial level will equal the peak JbP plus the pressure exerted by the column of blood lying between the right atrium and the lower surface of the air collection. In numerical terms,

$$y - x = d - h,$$

where y = the peak CVP (in cm of blood), x = the peak JbP (in cm of blood), d = the vertical distance between the two transducers (in cm), and h = the effective height of the air column (in cm). Therefore,

$$h = d - (y - x),$$

$$h = d - \frac{1.36}{1.055} (\text{CVP} - \text{JbP}),$$

$$h = d - 1.29 (\text{CVP} - \text{JbP}),$$

where CVP and JbP are recorded in millimeters of Hg, 1.36 is the factor for converting millimeters of Hg to centimeters of H_2O , and the value 1.055 is used as the specific gravity of blood for converting centimeters of H_2O to centimeters of blood. Though the formula describes the vertical height of a single continuous column or the combined vertical height of separate

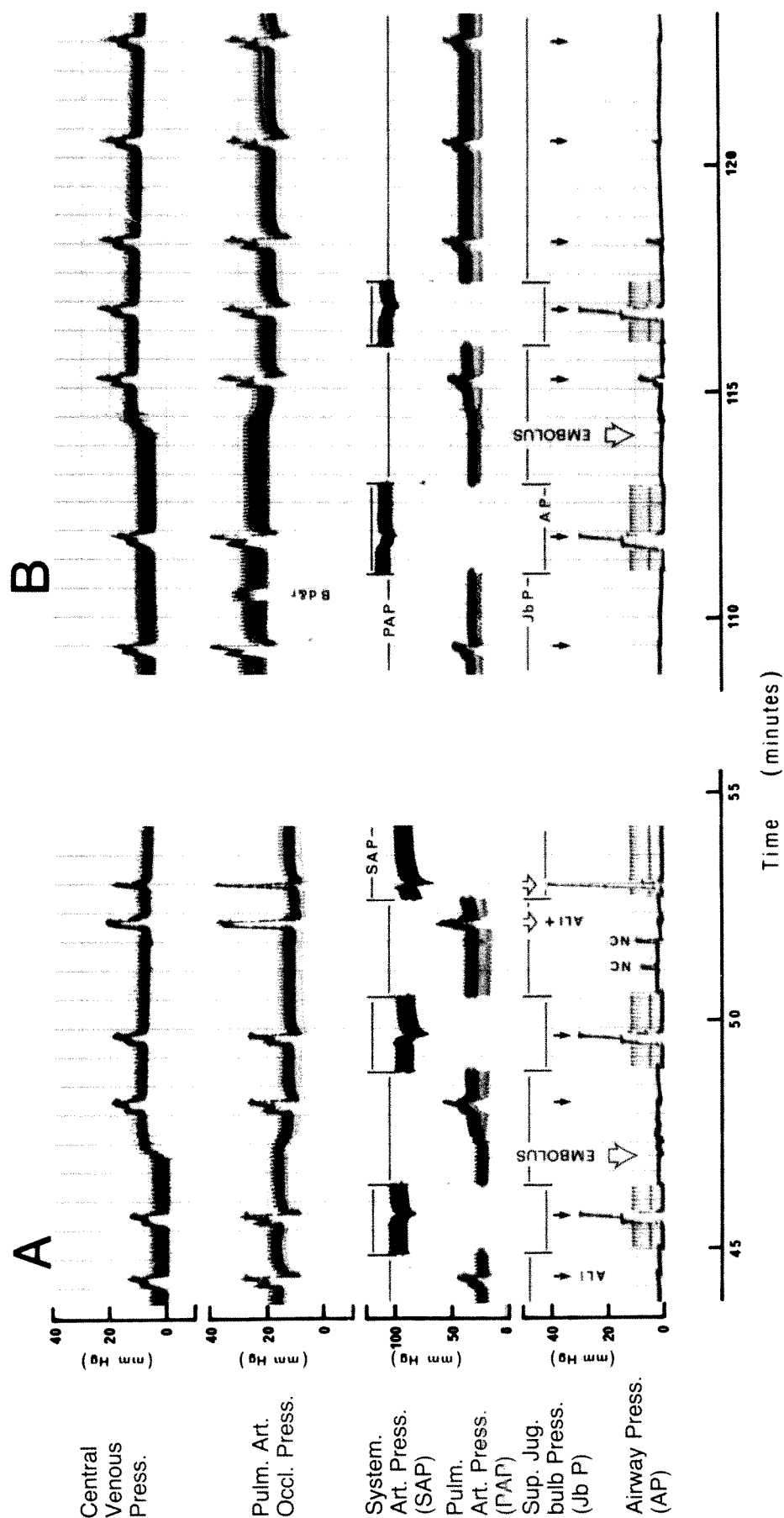


Figure 1. Sequence of ALL in animal 2 both before and after the injection into the great vein of the neck of 2 ml/kg air over 30 sec. **A** Before fluid loading with 20 ml/kg Dextran 70. Abbreviations: ALL, active lung inflation (indicated by small, filled arrows) to a peak airway pressure of 4 kPa (30.0 mm Hg); ALI +, active lung inflation to a peak pressure of 5.5 kPa (41.3 mm Hg) (it will be apparent from the CVP and PAOP tracings that these two inflations were performed for differing lengths of time); NC, manual neck compression, which, unlike ALL, was effective in raising the JbP in the absence of volume loading; B d&r, deflation and then reinflation of the balloon of the PAOP line.

Figure 4 demonstrates the (PAOP-CVP) difference, which is presented as an index of the transatrial pressure gradient, at the times A, B, C, and D above.

Table 1. Incidence, Magnitude, and Duration following Air Embolism of Peaking of the JbP Associated with an ALI of 4 kPa

	Air embolus at low CVP	Repeat embolus at low CVP	Air embolus at high CVP	Repeat embolus at high CVP
Total number of sheep	9	3	8	3
Number of sheep in which ALI produced peaking of JbP	0	1 ^a	8	3
Magnitude of the first and highest peaks of JbP (mm Hg) (relative to superior jugular bulb level) ^b	N/A	7.5	9.6 ± 5.5	12.0 ± 6.1
Magnitude of the corresponding peaks of CVP (mm Hg) (relative to right atrial level)	12.9 ± 1.7	16.5 ± 1.8	26.1 ± 2.5	29.6 ± 1.2
Length of time that peaking of the JbP was present (min)	N/A	8.0	22.4 ± 21.2	13.3 ± 9.3
Calculated effective height of the collection of air (cm) (see Fig. 3)	N/A	10.8	14.5 ± 5.1	12.6 ± 5.8

^aIn this sheep the CVP at the time of the repeat embolus was still elevated from the previous embolus.^bThe difference in vertical height of the CVP and JbP transducers (for the group of eight sheep) was 36.1 ± 2.2 cm.

In the groups of nine and eight sheep undergoing a single 2 ml/kg embolus before and after, respectively, the elevation of the CVP, there was a statistically significant reduction in the (PAOP – CVP) difference as a consequence of the air embolus alone (i.e., time C compared with time A) ($P < 0.01$). There was a further significant decrease in the (PAOP – CVP) difference during the release phase of ALI (i.e., time D compared with time C) ($P < 0.01$). Elevation of CVP did not in this study have a statistically significant effect on the (PAOP – CVP) difference after air embolism (i.e., time C compared with time C, and time D compared with time D, comparing data from the same eight sheep and excluding animal 4, which died before elevation of the CVP). Reversal of the (PAOP – CVP) difference occurred in eight situations in five different sheep. The mean magnitude of the reversed gradient was 2.4 ± 1.4 mm Hg.

Sheep 4 suffered a cardiac arrest after the air embolus at low CVP was repeated. The pulmonary artery pressure first rose and then fell, and within a minute of the completion of the air injection the tracings of central venous and pulmonary arterial pressure were identical. The animal could not be repositioned quickly enough to permit resuscitation. The remaining sheep all awoke soon after the completion of the anesthetic and showed no apparent ill effects.

Discussion

In most instances in the present study the peaks of venous pressure seen with ALI could not have been transmitted from right atrial level to jugular bulb level without the presence of a collection or collections of air or bubbles of air in the superior vena cava and the

great vein of the neck. The presence of such collections has been clearly demonstrated in another study in "upright" sheep (19) and was confirmed on several occasions in the present study by the free aspiration of air from the upper part of the SVC and from the neck vein cannula. Air can also collect in appreciable volumes in the large veins of patients, positioned either head down (20,21) or head up (2,14,15).

Transmission of venous pressure upward through an air collection, without the expected falloff in hydrostatic pressure with height (19), is no doubt the mechanism by which ALI generated peaks of CVP can be accompanied by simultaneously occurring peaks of JbP. In the present study these peaks in JbP occurred only when the CVP was elevated before the injection of air. It is suggested that the increased CVP plus transmission of pressure upward through air collected in the SVC resulted in turn in an increase in intraluminal pressure in the lower part of the great vein of the neck. Consequent distension of the neck vein permitted air to collect within it also. In fact, aspiration from one neck vein, distended and pulsing with the venous pressure, returned 15 ml of blood containing 10 ml of air as large bubbles.

In patients undergoing neurosurgery in the sitting position, the presence of temporary collections of air in the upright SVC and neck veins probably explains why the application of PEEP or ALI after the diagnosis of air embolism has resulted in visible (3–5) and even audible (2) escape of sometimes large volumes of air from open veins. In contrast, in the previously described animal models (1,11,12), only one of which included air emboli (1), the application of PEEP did not result in any increase in cerebral venous pressure.

In the present study the failure of ALI to result in an elevation of JbP when the air embolus was injected

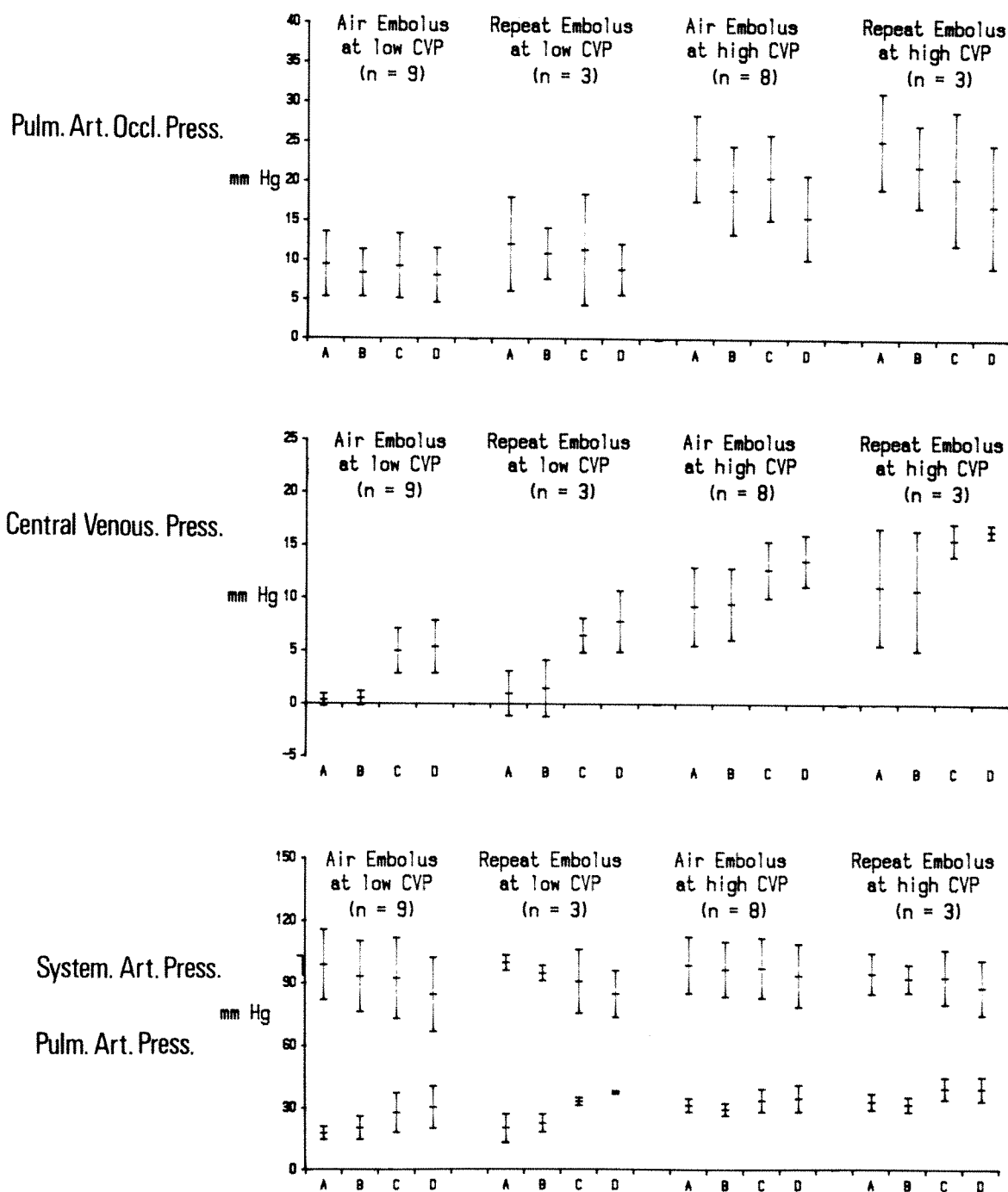


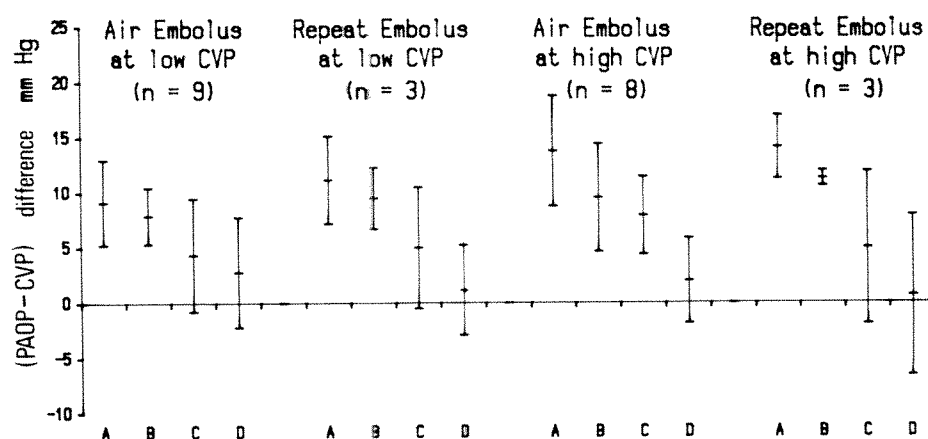
Figure 3. Vascular pressures (mean $\pm$ SD) before and after air embolism and before and during the release phase of an ALI of 4 kPa (30.0 mm Hg). Time A, before air embolism and before ALI; time B, before air embolism and during the release phase of ALI; time C, after air embolism and before ALI; time D, after air embolism and during the release phase of ALI.

before the elevation of the CVP does not mean that all the air had necessarily carried immediately to the heart. Doppler verification of delayed cardiac passage

of air well after the completion of its injection into a systemic vein has been evident in those sheep we have assessed as in previous animal studies (16-19,22). As seen in Figure 2, if the peak CVP produced by ALI is low, the "effective height," h , of the air column necessary to result in an increase in JbP must be considerable.

The length of time that air persisted in the "up-right" veins in sufficient volume to transmit a peak

Figure 4. (PAOP - CVP) differences (mean $\pm$ SD) before and after air embolism and before and during the release phase of an ALI of 4 kPa (30.0 mm Hg). Time A, before air embolism and before ALI; time B, before air embolism and during the release phase of ALI; time C, after air embolism and before ALI; time D, after air embolism and during the release phase of ALI.



of CVP to the level of the jugular bulb varied in the different sheep from 1 min to more than 1 hr with a mean time of 22.4 min and was not related to the actual level of the raised CVP or to any other readily identifiable factor in this study. Most of the other factors that might influence the life of an air collection, namely, the diameter of the vessel, the rate of blood flow, the presence or absence of marked venous pulsation, the angle of inclination of the vessel, and the diameter of the air bubbles, have been discussed in some detail by Martin et al. (17). Although in our study cardiac output was not measured, it is difficult to imagine that the Dextran infusion could have consistently lowered the cardiac output: certainly the systemic arterial pressures remained notably unchanged.

The sheep that died demonstrated an initial increase in pulmonary artery pressure followed by a sharp decline. The CVP continued to increase until the tracings of pulmonary arterial and central venous pressures were identical. This situation has been described previously (1) and represents a failing right ventricle with tricuspid and pulmonary incompetence, with presumably acute dilation of the right side of the heart (23). It is suggested that a dilated and failing right ventricle with likely pulmonary and tricuspid valve incompetence is the likely mechanism of the so-called air lock effect, which is characteristically described as being associated with a rapid, large embolus (24,25). In a neurosurgical patient in the sitting position the risk of a massive, sudden embolus of sufficient volume to result in a dilated failing right ventricle may be reduced, the authors believe, if the CVP measured at right atrial level is maintained above 0.5 kPa. Air that enters the venous system is likely to result, as it does in sheep, in a loss of the hydrostatic pressure difference in the upright SVC and an elevation of the venous pressure high in the SVC (19). The higher this pressure in the upper SVC, the more

likely that the lower part of the internal jugular veins will distend, thus allowing air to collect in these vessels also. Loss of hydrostatic pressure difference in a vertically placed neck vein could in turn result in the venous pressure at the operation site ceasing to be subatmospheric. In this event air entry would be replaced by bleeding from the open vein.

It is not suggested that moderate elevation of CVP will prevent air reaching the heart, but it may reduce the risk of a massive, sudden, life-threatening embolus. The risk of air embolism may also be reduced by PEEP of 1 kPa or more (26-28). The present authors believe that any beneficial role of PEEP is likely to be related to its effect on CVP and the consequent tendency for air to collect also in distended neck veins.

The (PAOP - CVP) difference in the present study was reduced by air embolism and further reduced with ALI. The difference was reversed in eight different situations in five out of the nine sheep. This reversal of the normal "transatrial" pressure gradient was maximal immediately after release of the ALI, just as is the case in humans after release of a Valsalva maneuver (6-8). Cucchiara et al. using two dimensional transesophageal echocardiography and covering the release phase of 2 kPa PEEP demonstrated paradoxical flow through an atrial defect in 3 out of 20 patients anesthetized in the sitting position (29).

The incidence of reversal of the (PAOP - CVP) difference was not influenced in this small study by the level of the CVP before the air embolus. This may not be the case with humans, for whom fluid loading has been recommended as a prophylactic measure against paradoxical embolism (30).

Throughout the present studies manual compression of the neck was used to demonstrate that an increase in venous pressure in the neck veins did in fact result in an increase in pressure recorded from the catheter located in the superior jugular bulb. It is

worth noting that neck compression reliably raised the JbP even in the absence of volume loading.

In conclusion, during neurosurgery in the sitting position, moderate elevation of the CVP may tend to promote the collection of air in large-diameter superiorly placed veins and thus may reduce the likelihood of a massive, sudden air embolus. Also, ALI after venous air embolism will probably help in identifying the site of air entry only when an appreciable column of air has collected in the upright systemic veins. Finally, ALI may well increase the likelihood of paradoxical embolism in patients at risk. Controlled inflation of a pneumatic neck cuff (1) is a more logical way of preventing further entry of air and of facilitating identification of its site of entry.

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Embolized Air Collection in the Superior Vena Cava of "Upright" Sheep

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Embolized air collection in the superior vena cava of "upright" sheep. *Anesth Analg* 1987;66:1135-40.

In 34 studies on six "upright" anesthetized sheep central venous pressure from sites in the upper and lower superior vena cava (SVC) was recorded before, during, and after the injection into a neck vein of 1-ml increments of air every minute for 15 min. After the injection of air, the pressure recorded from the upper site increased significantly. This increase was the result of air collecting in the SVC with a

consequent loss or partial loss of the SVC hydrostatic pressure difference. The time of onset and the duration of collection were not influenced by hyper- or hypovolemia nor by 1 kPa positive end-expiratory pressure. The readily identifiable change in the venous pressure in the upper SVC provided an earlier and more reliable warning of these small-volume air emboli than did a Doppler probe directed at the right side of the heart.

Key Words: EMBOLISM—air. NEUROSURGERY—sitting position.

Embolized air that has been reported to collect temporarily in the superior vena cava (SVC) of patients positioned upright (1,2) could result in a loss or partial loss of any hydrostatic pressure difference that in theory exists between different levels of a distended or partially distended vertically placed SVC.

In hydrostatic terms, the pressure within the lumen of an SVC distended with blood and free of air will be lower at a site just inside the thorax than at a site at right atrial level. If the difference in vertical height of the two sites is 7.5 cm, the difference in absolute pressures would be expected to be approximately 0.75 kPa, although this would not necessarily be the case if the SVC did not remain distended throughout its length and throughout the cardiac and respiratory cycles. When the differing absolute intraluminal pressures at two levels in a distended SVC are recorded using saline-filled manometer tubing and with both transducers positioned at right atrial level, then the two recorded pressures will be expected to be very much the same.

If embolized air does collect in a vertically positioned SVC and the intraluminal pressure is transmitted upward without the expected falloff in hydrostatic pressure, then the central venous pressure (CVP) recorded from a site high in the SVC will be higher

than that recorded from a site at right atrial level, assuming that both transducers are positioned at right atrial level and that the manometer tubing is saline filled.

The present study using anesthetized sheep positioned with the SVC as vertical as practicable was designed to answer several questions.

First, is there in fact an expected hydrostatic pressure difference between different levels of a vertically placed SVC and, if so, is this difference affected by factors that might influence SVC distension such as hyper- or hypovolemia or the presence or absence of a positive end-expiratory pressure (PEEP)? Second, does air injected distally into a neck vein collect temporarily in the upright SVC and, if so, does it produce a measureable change in the hydrostatic pressure difference recorded from two different levels in the SVC? Third, if air does collect in the SVC and does result in identifiable changes in the hydrostatic pressure difference, are the time of onset and the duration of the changes influenced by the level of the CVP before the injection of the air or by the presence or absence of 1 kPa of PEEP? Fourth, might an identifiable change in hydrostatic pressure due to air collecting in the SVC precede Doppler identification of air carrying to the heart?

Methods

Six fasting sheep with a mean weight of 39.5 kg were included in the various studies. They were anesthe-

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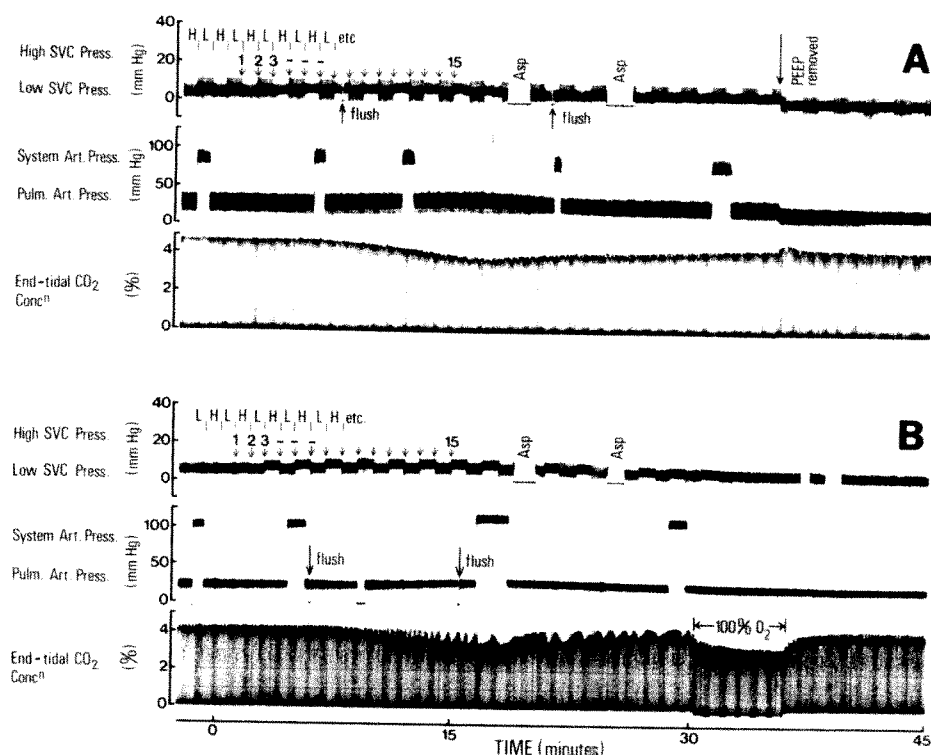


Figure 1. Continuous records from two separate studies made before, during, and after the injection into the great vein of the neck of 1-ml increments of air at 1-min intervals for 15 mins. The records show the venous pressure from the upper and lower SVC recorded alternately at 1-min intervals using a two-way stopcock to a single transducer, pulmonary artery pressure and systemic arterial pressure using a second transducer, and end-tidal CO₂ concentration. A) A 42-kg sheep during hypovolemia and 1 kPa PEEP. B) A 32-kg sheep during hypervolemia and without PEEP. Abbreviations: 1, 2, 3, ..., 15, injections of the first, second, third, and fifteenth 1-ml increments of air. H, L, H, L, H, etc., alternate recording of venous pressure from two sites high and low in the SVC (upper and lower SVC in text); Asp, the time of aspiration of 5 ml of blood + air from the sites in the lower and upper SVC.

tized with 25 mg/kg pentobarbital and artificially ventilated with 1-2% halothane and nitrous oxide and oxygen in a ratio 2:1. A constant tidal volume was delivered using a Manley ventilator with the fresh gas flow rate and the tidal volume set to maintain a respiratory rate of 12 breaths/min and an end-tidal CO₂ concentration of between 4 and 4.5%.

Catheters for monitoring pressure were placed in the main artery of the foreleg, the main pulmonary artery, the right atrium or adjacent proximal or "lower" SVC after withdrawal from the right ventricle, and the distal or "upper" SVC after withdrawal into the great vein of the neck and subsequent reinsertion to the point at which the pressure tracing moved freely with respiration. A catheter for introducing the air emboli was placed in the great vein of the neck distally and directed toward the base of the skull. Two additional catheters were placed in the great vein of the neck, one proximally in the "lower" neck vein after withdrawal from the chest and the other distally in the "upper" neck vein in the region of the superior jugular bulb (3). The catheters to the pulmonary artery and the sites in the upper and lower SVC were all inserted via the great vein on one side of the neck, while the catheters to the sites in the upper and lower neck vein and the catheter for injecting air were all inserted into the neck vein of the opposite side.

The sheep were positioned upright with the hind-

legs tucked under the body, the forelegs outstretched, the chest tilted 40° head up, the neck erect, and the head facing forward. End-tidal CO₂ concentration was monitored with a Godart Capnograph BE(17070), and a Doppler probe (MedaSonics model D8) was directed from the wool-free area under the right foreleg toward the right heart and its position verified by saline injection.

Upper and lower SVC pressures were recorded alternately at 1-min intervals via a two-way stopcock to a single transducer (see the venous pressure tracings in Fig. 1). Also recorded were end-tidal CO₂ concentration and pulmonary arterial and occasional systemic arterial pressures alternately via a second transducer. The two pressure transducers (Elcomatic EM 750) were placed at right atrial level; the recorder was an Elcomatic EM 740.

Air emboli 1 ml in volume were injected at 1-min intervals for 15 min via the catheter in the neck (see the arrows labeled 1 through 15 in Fig. 1). The injections were made over 2 sec at the time that the two-way stopcock was turned to record alternately the upper and lower SVC pressures. The two-way stopcock was turned at 1-min intervals throughout the duration of each study.

A total of 34 separate studies were performed, in random order, in six different situations, namely, hypovolemia after venesection of 10 ml/kg, normovo-

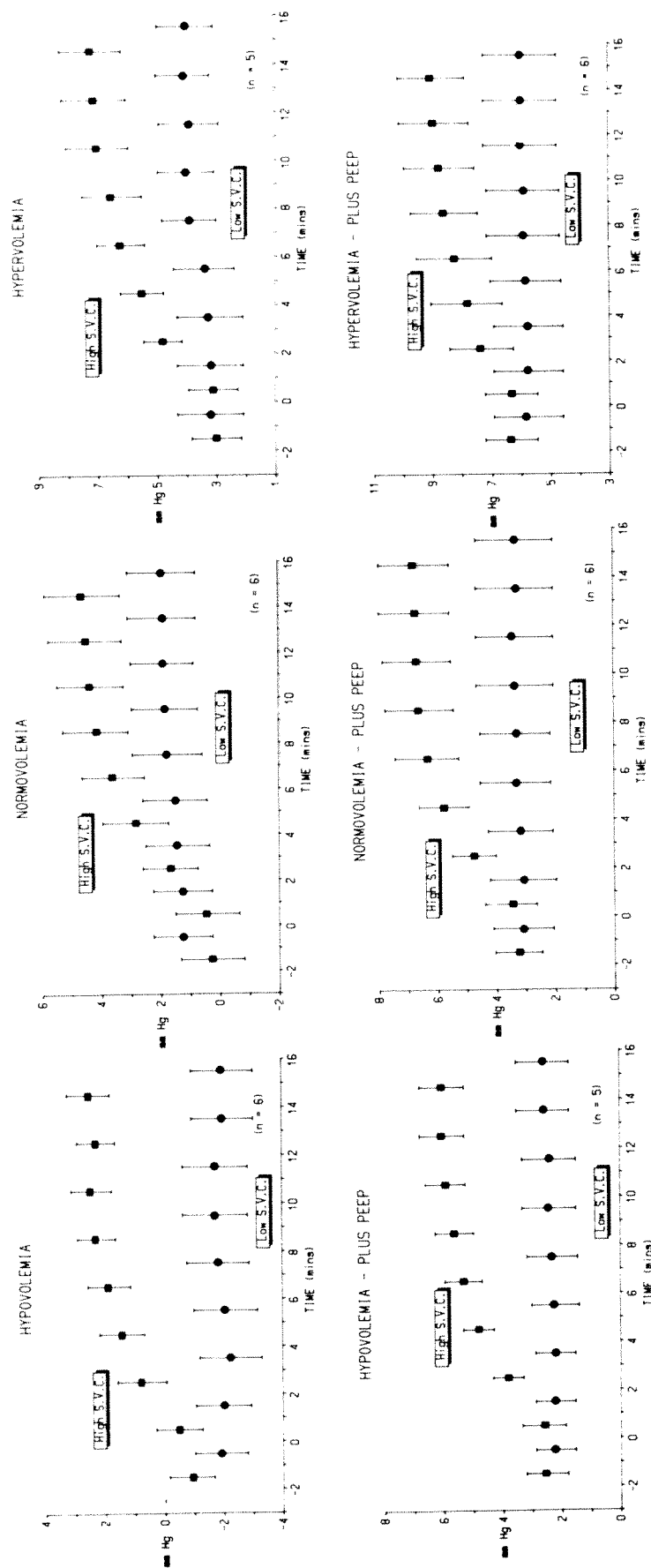


Figure 2. Mean ($\pm$ SEM) of the venous pressures at end expiration and in the y-descent phase of the venous waveform recorded from the two sites high and low in the SVC (upper and lower SVC in text). $\blacksquare$, The venous pressure from a site high in the SVC, $\bullet$, the venous pressure from a site low in the SVC. The first 1-ml increment of air was injected at time 0 min and the last (the 15th) increment at time 14 min.

Table 1. Frequencies of the Differing Durations of a Clinically Identifiable Change in the SVC Hydrostatic Pressure Difference

	Hypovolemia		Normovolemia		Hypervolemia	
PEEP (kPa)	0	1	0	1	0	1
"	6	5	6	6	4 ^a	5 ^a
Duration						
<10 min	0	1	1	0	0	1
10-20 min	1	0	0	0	1	0
>20 min (or >15 min + 100% oxygen)	5	4	5	6	3	4

^aIn two studies the duration of the change was not recorded.

lemia, and hypervolemia after transfusion of 10 ml/kg Dextran 70, all with and without 1 kPa PEEP.

In the last 22 studies, 5-ml volumes (sometimes including embolized air) were gently aspirated from the catheters lying in the upper neck vein, the lower SVC, the lower neck vein, and the upper SVC in that order. The aspirations were begun 2 min after the last (15th) increment of air and were completed over the ensuing 10 min.

The upper and lower SVC pressures, before and after the injection of air emboli, are presented for each of the six different situations as means $\pm$ SEM. Statistical analysis was performed using repeated measures analysis of variance. The protected least significant difference method was used to compare the two venous pressures before the introduction of air and to compare the changes in both these pressures that occurred after the introduction of air (4). Probability levels >0.05 were taken as not statistically significant.

Results

After the venous injection of air there was, in all studies, a readily identifiable change in the dynamic venous pressure record from the upper SVC compared to that from the lower SVC (see the two examples in Fig. 1). This change occurred in all studies within 5 min from the first 1-ml injection of air and within 3 min in 32 out of the total of 34 studies. Figure 2 shows the mean ($\pm$ SEM) of the upper and lower SVC pressures in the six different situations. (The upper and lower SVC pressures were quantified using the pressures recorded at end expiration and in the y-descent phase of the venous waveform for two reasons. Dynamic venous pressure recordings are necessary to confirm the continuing presence of the venous waveform and of pressure swings with ventilation. Second, the end-expiratory "diastolic" venous pressures are readily comparable when the record alternates from upper to lower SVC pressure, whereas alternating mean pressures are less so.) In each situation there was no significant difference in the two SVC pressures measured before the injection of air. How-

ever, within 3 min of the first injection of air there was in each situation a statistically significant increase in pressure recorded from the upper SVC. Within 7 min the level of statistical significance reached probabilities of <0.0001 in each of the six situations. No statistically significant changes in pressure were recorded in the lower SVC.

The duration of a clinically identifiable difference in the two dynamic SVC pressure tracings after the completion of the 15 incremental injections of air was >10 min in 29 of the 32 studies in which duration was recorded (Table 1) in spite of the aspiration of appreciable volumes of air in many of the studies. In 27 of the 32 studies an identifiable difference persisted for either >20 min or >15 min in studies in which the inspired oxygen was changed to 100% 15 min after cessation of air injection (Fig. 1B). When the inspired gas was changed to 100% oxygen 15 min after the last increment of injected air, the pressure difference reverted to its preembolus level within approximately 5 min.

The times at which air embolism was first identifiable using 1) dynamic SVC pressure recordings, 2) Doppler ultrasound, and 3) the onset of a definite decrease in the end-tidal CO_2 concentration are shown for the individual studies in Table 2. The onset of an increase in pulmonary artery pressure usually approximated closely with the onset of a decrease in end-tidal CO_2 concentration.

Gentle aspiration of 5-ml volumes from the four venous sites in the order described revealed air in 3 out of 10 successful aspirations from the upper neck vein, 8 out of 22 from the lower SVC, 16 out of 21 from the lower neck vein, and 10 out of 20 from the upper SVC. In the numbers studied there was no clear evidence that blood volume status or PEEP influenced the yield of air at aspiration.

Discussion

Before the introduction of a venous air embolus, the venous pressures recorded from two sites in the upper and lower SVC of upright sheep were similar.

Table 2. Frequencies of the Differing Times at Which Incremental Air Entry was First Identified

	Hypovolemia		Normovolemia		Hypervolemia	
PEEP (kPa)	0	1	0	1	0	1
<i>n</i>	6	5	6	6	5	6
Using identifiable changes in SVC hydrostatic pressure difference						
<1 min	4	0	2	3	1	0
1-3 min	2	5	4	3	3	5
3-5 min	0	0	0	0	1 ^a	1 ^a
Using Doppler ultrasound					(<i>n</i> = 4) ^a	(<i>n</i> = 5) ^a
<1 min	3	0	0	0	1	0
1-3 min	1	1	0	2	3	1
3-5 min	1	2	2	1	0	1
>5 min	1	1	4	0	0	3
Not diagnosed	0	1	0	3	0	0
Using end-tidal CO ₂ concentration					(<i>n</i> = 5)	(<i>n</i> = 6)
<5 min	0	0	0	0	0	0
5-10 min	5	1	0	0	1	0
>10 min	1	2	5	6	2	5
No fall	0	2	1	0	2	1

^aDoppler not available on day of these studies.

Because the pressures were recorded with saline-filled manometer tubing connected alternately to a single transducer, it is clear that the absolute intraluminal pressure in the upper SVC is lower than that at right atrial level and that the difference in absolute pressures is essentially a consequence of simple hydrostatic forces.

This hydrostatic pressure difference in the SVC before the introduction of air was found to exist not only in hypervolemic sheep in which the CVP was elevated and the SVC likely to be distended throughout its length, but also during hypovolemia with a lowered CVP and during the application of 1 kPa PEEP. There were, however, two of the six situations, namely, hypovolemia and normovolemia both without PEEP, in which the preembolus pressures recorded with a single transducer at right atrial level from sites in the upper and lower SVC were slightly though not significantly different from each other. In the hypovolemia situation, rapid ventricular filling after ventricular systole results in the y-descent of the venous pressure being more pronounced at right atrial level than at a site high in the SVC, whereas in the normovolemia situation it is suggested that the SVC may not always have remained fully distended throughout the cardiac and respiratory cycles and that the pressure high in the SVC could have been influenced by a negative intrapleural-mediastinal pressure.

With the introduction of very small volumes of air into a neck vein distally, the preembolus hydrostatic pressure difference in the upright SVC was removed or partly removed, and the venous pressure at end

expiration and in the y-descent phase measured from a site high in the SVC increased in an obvious and readily identifiable manner. The mean pressure when it was recorded also increased relative to the mean pressure at right atrial level.

The change in the hydrostatic pressure difference between two sites in the upper and lower SVC seen after the introduction of air can only be explained by the existence of a collection in the SVC of at least some of the injected air together with nitrous oxide that diffused into the collection.

The collection of air in the SVC and the great vein of the neck was confirmed in the latter part of the study by the aspiration, 2 to 12 min after the cessation of the air injections, of 5-ml volumes of blood with or without air from sites high and low in the SVC and high and low in the neck vein. Out of a total of 41 successful aspirations from two of the four sites, namely, the sites high in the SVC and low in the neck vein, 26 contained air. The fact that the other 15 aspirations failed to contain air even though there was persisting evidence of a loss of the hydrostatic pressure difference suggests that in these cases the catheter tip may have been lying within the flow of venous return rather than in or adjacent to an air collection.

After air injection, the time of onset and the duration of a readily identifiable increase in pressure in the upper relative to the lower SVC were not notably influenced by hypervolemia, hypovolemia, or the presence or absence of PEEP. The duration was >20 min, or >15 min in studies in which the inspired oxygen concentration was changed to 100%, in 27 out

of 32 studies and in spite of the aspiration of appreciable volumes of air in many.

The increase in pressure in the upper relative to the lower SVC after small incremental air emboli occurred either earlier than or at the same time as the appearance of identifiable Doppler evidence. Disappearance of Doppler evidence of air corresponded closely with the return to the preembolus state of the SVC pressure difference. The former finding suggests that small volumes of injected air may on occasion collect temporarily in the SVC before any air carries to the heart: the latter suggests that the Doppler will continue to identify air bubbles passing to the heart as long as air collections persist in the SVC. Doppler and transesophageal echocardiographic evidence of delayed cardiac passage of injected air has also been described in other animal models (5-7).

In the presence of PEEP, placement of the Doppler probe was often critical and even with optimal placement Doppler evidence of embolized air was absent in four studies and muffled and uncertain in several other studies. It is possible that such difficulties with Doppler diagnosis may be a consequence of the increased functional residual capacity with PEEP and may explain in part the reported reduced incidence of air embolism when 1 kPa PEEP is employed in neurosurgical operations in the sitting position (8-10). In one of the present studies in which PEEP was used, air embolism resulted in a change in the SVC pressure difference and a decrease in end-tidal CO₂ concentration but no discernable change in the muffled Doppler sounds until an inadvertent momentary release of the PEEP revealed typical Doppler evidence of air.

The release of PEEP at the end of a study was also associated in another two sheep with the momentary return of Doppler evidence of air after it had previously disappeared and after the SVC pressure difference had returned to its preembolus state. Perhaps in these two instances collected air had persisted longer in the neck veins than in the SVC. In patients undergoing neurosurgery in the sitting position, the onset (11) and return (12) of Doppler evidence of air has also been associated with the release or reduction of 1 kPa PEEP.

The clinical implications of the present study are the following. First, it is likely that embolized air will also collect temporarily in the SVC of patients undergoing neurosurgery in the sitting position, as has already been reported (1,2). Second, such collections of air, when they occur, will result in the loss or partial loss of the hydrostatic pressure difference in the upright SVC. Thus, if a CVP catheter is sited in the upper SVC, the pressure reading could be of the order of 5 mm Hg higher than the actual CVP

reading. Third, the use in clinical practice of two pressure readings from separate sites in the upper and lower SVC might be justified when early diagnosis of small volumes of embolized air is desired. With a double lumen catheter the possibility of the side hole of the catheter lying against the wall of the SVC should be borne in mind.

In conclusion, embolized air collects promptly and can persist for long periods in the SVC of upright sheep. The collections result in a readily identifiable increase in venous pressure in the upper SVC when compared with the pressure recorded from right atrial level. When the volume of embolized air is small, as was the case in this study, the SVC pressure changes consistently occur earlier or at the same time as Doppler evidence of air reaching the heart and well before changes are seen in end-tidal CO₂ or pulmonary artery pressure.

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Stimulatory Effects of Halothane and Isoflurane on Fluoride Release and Cytochrome P-450 Loss Caused by Metabolism of 2-Chloro-1,1-difluoroethene, a Halothane Metabolite

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BAKER MT, BATES JN, LEFF SV. Stimulatory effects of halothane and isoflurane on fluoride release and cytochrome P-450 loss caused by metabolism of 2-chloro-1,1-difluoroethene, a halothane metabolite. *Anesth Analg* 1987;66:1141-7.

The structural similarity of the halothane metabolite, 2-chloro-1,1-difluoroethene (CDE), to haloethenes that are metabolized by and inactivate cytochrome P-450, suggests that CDE may undergo secondary metabolism and degrade these isozymes. This possibility was examined in hepatic microsomes by determining fluoride release and cytochrome P-450 loss due to CDE metabolism in the presence of several anesthetics. CDE alone decreased cytochrome P-450 from phenobarbital-treated rats by as much as 37%, but the ad-

dition of isoflurane or halothane to incubations containing CDE increased the loss of cytochrome P-450 nearly twofold. Fluoride release was enhanced approximately 2.5 to 3 times by halothane or isoflurane; however, fluroxene inhibited fluoride release and did not enhance the loss of cytochrome P-450. Extrapolation of these results to the clinical situation suggests that the metabolism of CDE produced during halothane anesthesia and the accompanying cytochrome P-450 loss may contribute to the inhibition of drug metabolism produced by halothane.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane, fluroxene. BIOTRANSFORMATION, ANESTHETIC—halothane, isoflurane, fluroxene. ENZYMES—cytochrome P-450.

The metabolism of halothane has undergone considerable study in regard to its pathways and mechanisms of biotransformation. The importance of halothane metabolism lies in the fact that experimentally, reactive intermediates generated from its primary metabolism via either oxidative (1,2) or reductive pathways (3-5) have been implicated in its hepatotoxicity. Secondary halothane metabolism has received less consideration largely because of the low levels of halothane metabolites in the body and the expected inability of these compounds to form reactive metabolites.

Several studies of the *in vivo* metabolism of halothane have, however, led investigators to hypothesize that the reductive metabolite of halothane, 2-chloro-1,1-difluoroethene (CDE) may undergo secondary metabolism (6,7). Two possible mechanisms for this

include conjugation of CDE with glutathione catalyzed by glutathione transferase (8), and oxidation of CDE by cytochrome P-450. Evidence supporting a role of cytochrome P-450 in CDE metabolism is the release of fluoride ions that occurs upon incubation of CDE with hepatic microsomes under oxidative conditions (6,9). *In vivo*, the possible significance of CDE cytochrome P-450 metabolism, if it occurs, is again diminished by the fact that fluorinated ethene-induced hepatotoxicity has not been reported.

In spite of this, fluorinated ethenes are effective in inactivation of cytochrome P-450. This is a property common to many haloethenes. For example, inhibition of cytochrome P-450 has been demonstrated with vinyl and vinylidene fluoride (10), as well as with the chlorinated analog of CDE, trichloroethene (TCE) (11). The structural similarity of CDE to the haloethenes that are proven inactivators of cytochrome P-450 suggests that cytochrome P-450 destruction is also a consequence of CDE metabolism. Furthermore, CDE metabolism may occur *in vivo* and may thus contribute to the loss of cytochrome P-450 thought to be due to the primary reductive metabolism of halothane in exposed individuals (12,13).

The aims of the present study, therefore, were to evaluate the cytochrome P-450 inactivating properties

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Table 1. The Release of Fluoride and Cytochrome P-450 Loss by CDE Metabolism in Microsomes from Phenobarbital-Pretreated Rats^a

Incubation	nmol fluoride	nmol cytochrome P-450	nmol cytochrome P-450
	nmol cytochrome P-450	nmol cytochrome P-450	microsomal protein
	nmol cytochrome P-450	nmol cytochrome P-450	(% loss)
Blank (-NADPH)	0.24 ± 0.04		
Blank (-CDE)			1.74 ± 0.01
CDE, O ₂	16.64 ± 0.22		1.10 ± 0.01 (37) ^b
CDE, N ₂	1.75 ± 0.08		1.16 ± 0.01 (33) ^b
CDE, CO	1.08 ± 0.06		1.45 ± 0.02 (17)
CDE, O ₂ , isoflurane (2.0%)	37.36 ± 0.79		0.64 ± 0.01 (63)
CDE, N ₂ , isoflurane (2.0%)	8.16 ± 0.34		1.20 ± 0.03 (31) ^b
CDE, CO, isoflurane (2.0%)	4.82 ± 0.45		1.21 ± 0.03 (30) ^b

^aIncubations for fluoride determinations contained in 2 ml (3 mg/ml), 1 μ mol CDE, and 2 μ mol (1.0%) isoflurane where indicated. Incubations for cytochrome P-450 determinations contained 5 μ mol CDE or isoflurane (2.0%) in 2.5 ml of 5-mg/ml microsomal suspension. All incubations were carried out for 30 min. Values represent the means and standard errors of triplicate determinations. O₂, N₂, or CO (carbon monoxide) indicates a 100% atm of each gas. In this manuscript the value in parentheses after the anesthetic added to each incubation represents the pre-equilibration volume percent of anesthetic in the gas phase.

^bWithin each column values marked were not significantly different ($P > 0.01$). All other comparisons were significantly different.

of CDE in hepatic microsomes, and to assess the metabolism of CDE under conditions where CDE is formed from halothane. Specifically, the objectives were, 1) to evaluate the metabolism of CDE by fluoride release and determine the ability of CDE to inactivate cytochrome P-450; 2) to assess the effects of oxygen levels on metabolism of CDE; and 3) to evaluate the effects of halothane and other anesthetics on these processes. The results show that CDE inactivates cytochrome P-450, and the nonethenic anesthetics, halothane and isoflurane, have a stimulatory rather than an inhibitory effect on CDE metabolism and cytochrome P-450 loss.

Materials and Methods

Hepatic microsomes were prepared from male Sprague-Dawley rats, 210–250 g, purchased from Harlan Industries. The animals were fed a standard laboratory chow diet and some were allowed access to 0.2% sodium phenobarbital in their drinking water for 4 days before being killed. Microsomes were prepared by differential centrifugation and stored in 0.1 M Tris-HCl, 1 mM EDTA, pH 7.5, at -70°C before use.

Chemicals—CDE was purchased from SCM Specialty Chemicals (Gainesville, FL). Flame Ionization Detection gas chromatography indicated a CDE purity of >99%. Likewise, GC-mass spectral analysis of CDE gas dissolved in hexane revealed no contaminants. Halothane, isoflurane, and fluroxene were anesthetic grade compounds obtained from commercial sources.

Incubations—Microsomal incubations consisted of 2 or 2.5 ml of microsomes at 3 or 5 mg microsomal protein/ml in 0.1 M Tris-HCl buffer (pH 7.5) containing 1 mM EDTA. Incubations were performed in 9-

ml glass hypovials or 7-ml plastic vials (for fluoride assays) sealed with hycar septa. An NADPH generating system, consisting of 0.8 units glucose-6-phosphate dehydrogenase, 4.6 μ mol glucose-6-phosphate and 1.8 μ mol NADP, was added to the microsomes. The vials were then flushed with 100% oxygen (O₂) or oxygen-nitrogen mixtures for 2 min at a flow rate of approximately 1 L/min before sealing. Medical grade oxygen and prepurified nitrogen (N₂) were mixed in an anesthesia machine and the concentration of each gas was determined with a Perkin Elmer model 1100 Medical Gas Analyzer. In those incubations intended to be anaerobic, the vials were flushed with nitrogen for 6 min each. All incubations were carried out under 100% oxygen, except where specified. CDE was added by injecting a quantity of pure gas using a gas-tight syringe or where indicated by injecting CDE dissolved in ethanol. Halothane, isoflurane, and fluroxene were added as gases by injecting aliquots of oxygen saturated with each anesthetic at room temperature or as an ethanol solution where indicated. Incubations were initiated by placing the vials in a Dubnoff metabolic incubator at 37°C and stopped by placing the vials on ice.

Microsomal protein concentrations were determined by the method of Lowry et al. (14). Cytochrome P-450 and microsomal heme were measured spectrally as described by Omura and Sato (15). Cytochrome P-450 was assayed following formation of the reduced carbon monoxide-cytochrome P-450 complex, and microsomal heme following formation of the reduced pyridine-heme complex. Fluoride was determined with ion specific electrodes (Orion) as previously described (16).

Data were analyzed using unpaired Student's *t*-test

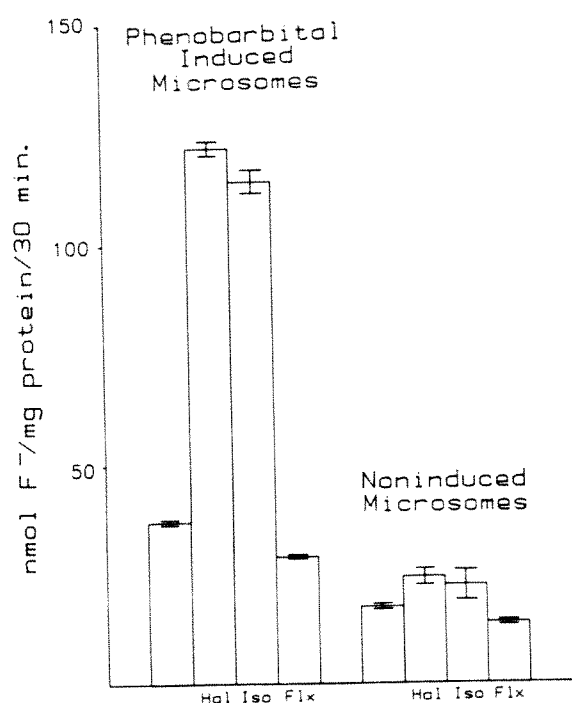


Figure 1. The effects of anesthetics on fluoride release due to CDE metabolism by microsomes from noninduced and phenobarbital-induced rats. Incubations contained 2 ml of microsomes (3 mg/ml) and 1 μ mol CDE and 2 μ mol (1.0%) of anesthetic added as ethanol solutions (1.4–2 microliters). Hal (halothane), Iso (isoflurane) or Flx (fluroxene) indicate the anesthetic added in addition to CDE. Values represent the mean and standard errors of triplicate determinations.

or one-way analysis of variance with the Newman-Keuls test, as appropriate. A value of $P < 0.01$ was considered statistically significant.

Results

The release of fluoride due to incubation of CDE in the presence of phenobarbital-induced microsomes is shown in Table 1. Fluoride release required NADPH, and was inhibited by carbon monoxide and anaerobic conditions. Addition of isoflurane, an anesthetic that is not metabolized under reductive conditions and only to a minor extent under oxidative conditions (17), stimulated the release of fluoride approximately two-fold. This fluoride release was also dependent on oxygen and inhibited by carbon monoxide. The defluorination of CDE in microsomes from untreated and phenobarbital pretreated rats is shown in Figure 1. Halothane, as well as isoflurane, caused significant enhancement of fluoride release in these incubations. Fluroxene did not stimulate fluoride release. The microsomes from phenobarbital-pretreated rats that contained 2.01 nmol cytochrome P-450/mg, liberated 2 to 4 times the fluoride released in the noninduced mi-

Table 2. The Effects of Anesthetics on the Loss of Cytochrome P-450 and Heme in Phenobarbital-Induced Microsomes Due to the Metabolism of CDE^a

Incubation	nmol/mg Protein $\pm$ SE (% Loss)	
	Cytochrome P-450	Heme
Blank (+CDE)	1.72 $\pm$ 0.01	2.12 $\pm$ 0.02
CDE	1.33 $\pm$ 0.02 (23) ^b	1.73 $\pm$ 0.06 (18)
CDE, halothane (1.6%)	0.79 $\pm$ 0.01 (54) ^c	1.48 $\pm$ 0.01 (31) ^b
CDE, isoflurane (1.6%)	0.73 $\pm$ 0.02 (57) ^c	1.50 $\pm$ 0.02 (29) ^b
CDE, fluroxene (1.6%)	1.26 $\pm$ 0.01 (27) ^b	1.92 $\pm$ 0.02 (09)

^aIncubations contained in 2.5 ml, 5 mg/ml microsomal protein, 2 μ mol CDE and 4 μ mol (1.6%) of each anesthetic. Incubations were carried out at 37°C for 30 min.

^bWithin each column, values marked with the same symbol were not significantly different ($P > 0.01$). All other comparisons were significantly different.

croosomes (0.6 nmol cytochrome P-450/mg). As reported previously, incubation with halothane (16) and fluroxene (18) with microsomes under oxygen releases negligible amounts of fluoride, and the amount produced during incubation with isoflurane is also minimal (<0.6 nmol/30 min⁻¹·mg⁻¹) (19).

Table 1 also shows the effects of CDE metabolism on cytochrome P-450 levels in microsomes from phenobarbital-pretreated rats. Incubation of CDE alone in the microsomes resulted in a decrease of cytochrome P-450 equivalent to a 37% decline. The addition of isoflurane to these CDE-containing incubations, which enhanced fluoride liberation, resulted in an approximately 70% greater loss of cytochrome P-450. A nitrogen atmosphere as well as CO were protective of cytochrome P-450. As shown in Table 2, the addition of halothane or isoflurane caused a near twofold greater loss of cytochrome P-450 than with CDE alone, whereas fluroxene addition did not result in further cytochrome P-450 loss. The losses of cytochrome P-450 in these studies occurred with proportionate declines in microsomal heme. In microsomes from untreated rats, cytochrome P-450 decreased from 0.61 to 0.47 nmol cytochrome P-450/mg on incubation with 5 μ mol CDE/2.5 ml microsomes (4 mg/ml) for 30 min under oxygen (duplicate determinations). Incubation of 5 μ mol of halothane, isoflurane, or fluroxene alone with phenobarbital induced microsomes (2.5 ml, 5 mg/ml) for 30 minutes in the presence of oxygen resulted in cytochrome P-450 levels of 1.86 ± 0.02 , 1.91 ± 0.01 , and 1.82 ± 0.03 nmol cytochrome P-450/mg, respectively. The initial levels were 1.93 ± 0.01 nmol/mg. Oxidation of CDE-containing microsomes with 1 mM $K_3Fe(CN)_6$ before assaying for cytochrome P-450 did not affect the measurable amount of cytochrome P-450. This indicates that no reduced complexes were formed between CDE and cytochrome P-

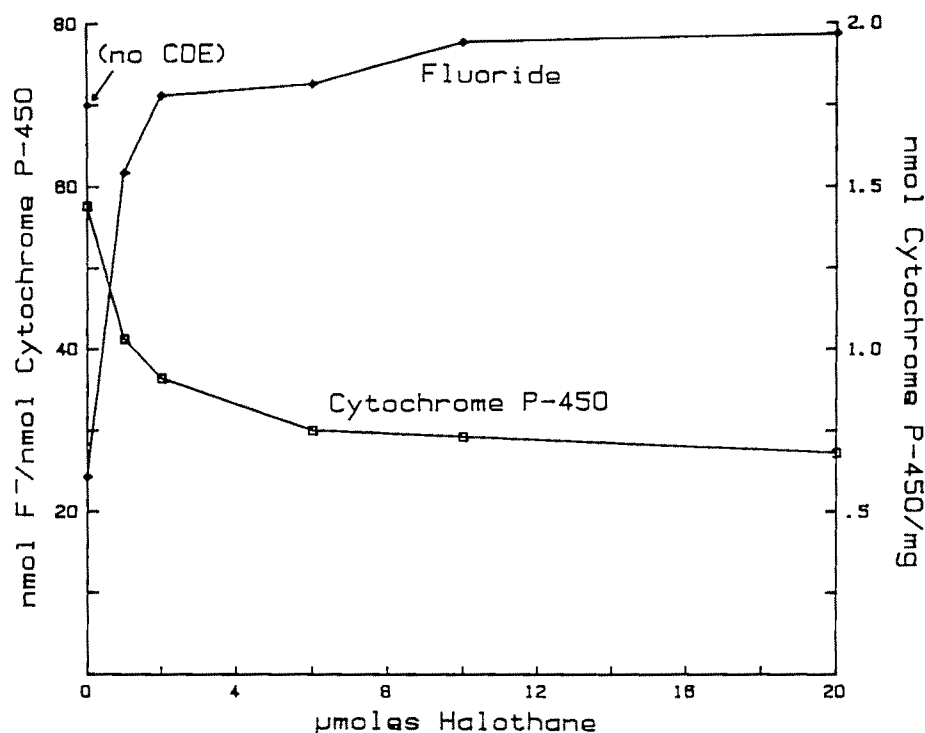


Figure 2. The effects of increasing amounts of halothane on fluoride release and cytochrome P-450 loss due to the metabolism of CDE. Incubations were carried out for 30 min and contained in 2 ml, 10 mg microsomes from phenobarbital treated rats and 4 μ mol CDE. (no CDE)—represents the cytochrome P-450 level after incubation of microsome with NADPH, but without CDE.

450 that interfered with binding of carbon monoxide to cytochrome P-450.

The relations of the relative concentrations of CDE to halothane and the stimulatory effects of halothane on CDE metabolism are shown in Figures 2 and 3. In the microsomes containing 5 μ mol CDE, the addition of as little as 1 μ mol halothane stimulated fluoride release and cytochrome P-450 inactivation (Figure 2). Furthermore, the addition of as much as 20 μ mol halothane did not inhibit fluoride release. Figure 3 shows the stimulation of CDE metabolism by halothane at various levels of CDE. Five-minute incubation periods were used here to minimize substrate depletion at low CDE levels, and because incubations using 2 μ mol of CDE near optimal fluoride release occurred in 10 minutes. As indicated, stimulation occurred with the addition of as little as 30, to as much as 2000 nmol of CDE to the microsomes.

The influence of oxygen levels on CDE metabolism is shown in Figure 4. At all oxygen levels, fluoride release increased in the presence of isoflurane or halothane. Also, nearly the same quantities of fluoride were measured from 5 to 21% oxygen in these studies. Only when attempts were made to make these incubations anaerobic did the release of fluoride sub-

Figure 3. The effects of halothane on the release of fluoride due to CDE metabolism resulting from the addition of various amounts of CDE. Incubations, carried out for 5 min, contained 6 mg microsomes in 2 ml from phenobarbital-treated rats and 2 μ mol (1.0%) halothane where indicated.

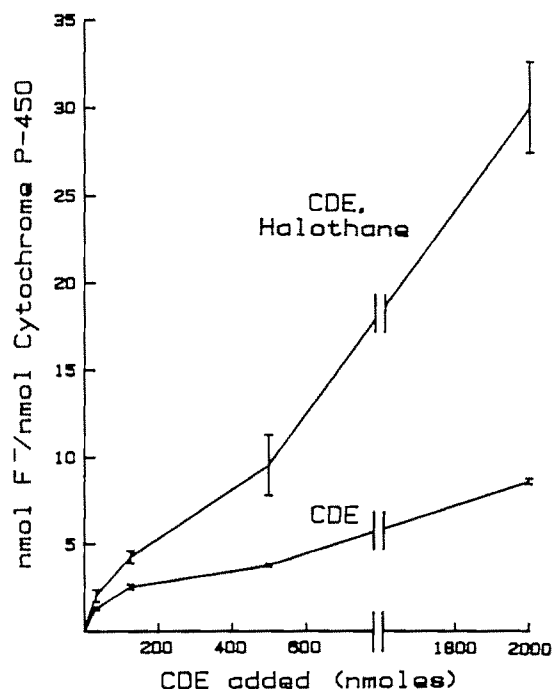
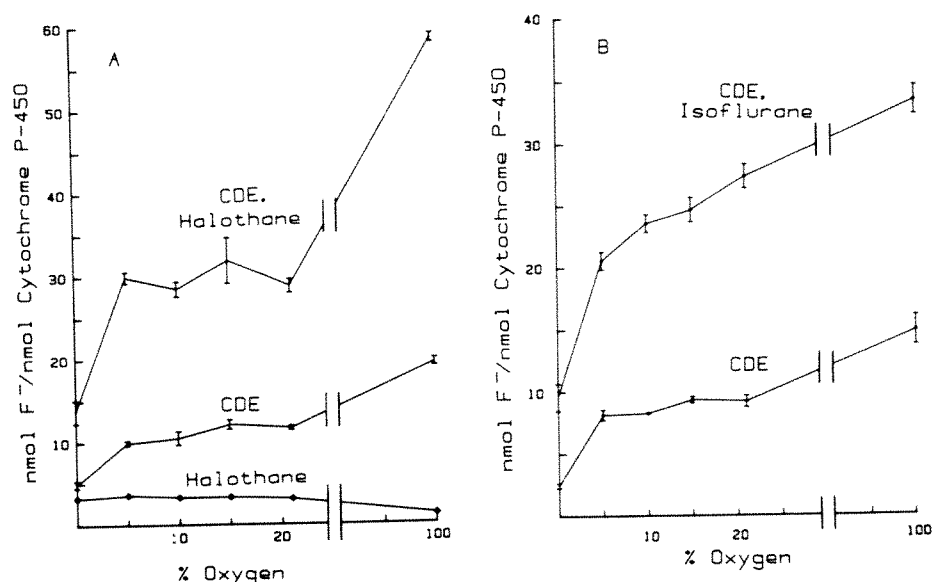


Figure 4. The effects of oxygen on the liberation of fluoride from the metabolism of CDE in the absence and presence of halothane (A) and isoflurane (B). Incubations contained, in 2 ml, 6 mg microsomal protein from phenobarbital-treated rats and 1 μ mol CDE, and 1 μ mol (0.5%) halothane or 2 μ mol (1.0%) isoflurane where indicated. Incubations were carried out for 30 min at 37°C.



stantially decline. The lack of total inhibition of fluoride release by nitrogen could be due to residual dissolved oxygen in these microsomes. It should also be noted that oxygen levels in the vials under the particular incubation conditions used could decline during the incubation period and become lower than the initial levels indicated.

Discussion

The halothane metabolite, CDE, is shown in this study to be an effective inactivator of cytochrome P-450. Its metabolic reaction with cytochrome P-450 to release fluoride, and the metabolism-dependent nature of the cytochrome P-450 inactivation process is demonstrated by the fact that these activities are induced by phenobarbital, they require NADPH, and they are inhibited by carbon monoxide. The concurrent loss of microsomal heme and cytochrome P-450 also provides evidence that the mechanisms of cytochrome P-450 destruction by CDE are similar to those proposed for other haloethenes. That is, upon their oxidation by cytochrome P-450, ethenic halocarbons are thought to destroy the cytochrome P-450 porphyrin ring by reactions of intermediate radicals or cations derived from the ethenes with the cytochrome P-450 heme moiety (10,20,21).

The effects of anesthetics on these processes in microsomes demonstrate that the metabolic reactions of CDE are modulated by other halocarbons. Rather than exhibiting inhibitory effects, halothane and isoflurane stimulate both fluoride release and destruction of cytochrome P-450 by CDE. It may be concluded that the

action of these anesthetics is to increase the total metabolic rates of CDE rather than alter its metabolic pathways. The uniqueness of these interactions is that isoflurane (17,18) and, to a greater degree, halothane, are also metabolized by the phenobarbital-induced forms of cytochrome P-450 (22). Therefore, apart from the stimulatory effects, the lack of inhibition alone suggests that different modes of interaction between CDE and these anesthetics occur with cytochrome P-450.

Although these stimulatory effects were substantial and support the hypothesis of secondary CDE metabolism, the possible mechanisms involved in these interactions are unknown. Stimulation of microsomal drug metabolism by volatile anesthetics (23,24) and solvents (25) has been reported previously, but these stimulatory effects were specific for certain substrates. For example, halothane enhances the hydroxylation of aniline in hepatic microsomes, but not the metabolism of aminopyrine, hexobarbital, or pentobarbital (23,24). Because halothane does not stimulate cytochrome P-450 drug metabolism as a whole, the anesthetics in the present study may act on the microsomal membranes or the cytochrome P-450 molecule itself in such a manner as to specifically alter the interactions of CDE with the cytochrome P-450 active sites.

The structural features of the anesthetics that produce stimulation are also unclear. Stimulation appears to be a somewhat nonspecific property of halocarbons because enhancement of CDE metabolism was not limited to the halogenated ethane, halothane, or to the halogenated ether, isoflurane, and occurred

with the nonfluorinated compound 1,1,1-trichloroethane (data not shown). Similar stimulatory effects were seen with enflurane, but the interpretation of this result is more difficult because enflurane releases significant fluoride under oxidative metabolizing conditions (19). Fluroxene, on the other hand, did not exhibit this stimulatory effect, which may be related to its ethenic moiety. The unsaturated carbon-carbon bond may allow this compound to compete effectively with CDE binding to cytochrome P-450 active sites. Alternatively, the inhibition may be associated with the ability of fluroxene to inhibit cytochrome P-450 (26,27).

Consistent with the mechanisms for cytochrome P-450 destruction by ethenic compounds, this study also shows that oxygen is involved in the metabolism and cytochrome P-450 destructive effects of CDE. However, although inhibition of fluoride release could be achieved by attempting to make the incubations anaerobic, decreasing the oxygen content from 21 to 5% had little effect on fluoride release, even in the presence of isoflurane or halothane. A nitrogen atmosphere also only partially blocked cytochrome P-450 inactivation. These findings, along with the fact that near optimal release occurs in a 10-min incubation period, shows that the interaction of CDE with cytochrome P-450 to release fluoride and inhibit cytochrome P-450 is rapid and can occur with a minimum of oxygen. From these data it cannot be conclusively ruled out, however, that anaerobic mechanisms do not make a contribution to these effects.

In summary, this study demonstrates the ability of CDE to effectively destroy cytochrome P-450 and the unique effects of the nonethenic anesthetics to stimulate this metabolism. These results, coupled with the apparent low oxygen requirements for CDE metabolism and cytochrome P-450 destruction, indicate that the metabolism of CDE following its formation from halothane in vivo is a viable metabolic pathway. This metabolism may contribute to the loss of hepatic cytochrome P-450 and therefore the inhibition of drug metabolism observed in vivo due to halothane exposures in experimental animals (28,29). Further studies need to be carried out to determine the specificity of destruction of cytochrome P-450 isozymes by CDE, and the mechanisms and scope of the effects of anesthetics on the interaction of CDE and other drugs with cytochrome P-450.

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Incidence of Hypotension Associated with Epidural Anesthesia Using Alkalinized and Nonalkalinized Lidocaine for Cesarean Section

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PARNASS SM, CURRAN MJA, BECKER GL. Incidence of hypotension associated with epidural anesthesia using alkalinized and nonalkalinized lidocaine for cesarean section. *Anesth Analg* 1987;66:1148-50.

The onset of epidural anesthesia is accelerated by alkalinization of lidocaine with added epinephrine (LE). The possibility that decreases in systolic blood pressure (SBP) are also enhanced was studied in 21 patients having elective cesarean sections. Ten patients given LE + NaHCO₃ (0.1 mEq/ml anesthetic solution) compared with 11 given LE alone had significantly ($P < 0.05$) greater decreases in SBP

(32% vs 19% from baseline values), as well as a greater rate of SBP decline to those minimum values (9%/min vs 3%/min, respectively). These differences were noted despite the fact that patients given LE + HCO₃ received no less ephedrine and no more additional anesthetic than controls. Possible adverse effects of SBP reduction on uteroplacental blood flow suggest that caution be used in the use of alkalinized LE in obstetrical patients.

Key Words: ANESTHETIC TECHNIQUES—epidural. ANESTHETICS, LOCAL—lidocaine. ANESTHESIA, obstetrical.

Epidural anesthesia is often preferred over spinal anesthesia for cesarean section because of its more gradual and more predictable onset of action. A major disadvantage of spinal anesthesia is a marked decrease in cardiac output and blood pressure resulting from the rapid onset of a high sympathetic block and decrease in venous return. Epidural anesthesia has been preferred in cesarean sections because it is believed that hypotension occurs less precipitously, thereby allowing it to be more easily treated or prevented (1).

The onset of epidural anesthesia is significantly accelerated by the use of alkalinized lidocaine (2,3), similar to the shortened onset and improved quality of anesthesia reported with carbonated lidocaine (4,5). The present study was undertaken to determine whether epidural alkalinized lidocaine with its more rapid onset of action also is associated with a higher incidence of hypotension than is epidural nonalkalinized lidocaine in patients undergoing elective cesarean sections.

Methods

Twenty-one ASA I-II full-term unpremedicated patients undergoing elective cesarean section were studied in a randomized, double-blind fashion. Patients with a history of hypertension or preeclampsia were excluded from the study. The protocol was approved by the Institutional Review Board for Human Research and written informed consent was obtained from all subjects. All patients were hydrated with 1.5 L Ringer's lactate solution IV. Baseline blood pressure was then recorded with an automated oscillometric blood pressure device (Dinamapp). The epidural space was located in the sitting position using a loss of resistance technique. Ten patients received a solution of commercially prepared 2% lidocaine plus 1:200,000 epinephrine with 1 mEq NaHCO₃ added freshly per 10 ml of anesthetic solution (pH 7.0), while 11 patients were given nonalkalinized commercial 2% lidocaine plus 1:200,000 epinephrine (pH 4.5). A test dose of 3 ml was injected and, if no change in pulse rate and no symptoms of a subarachnoid injection occurred, 15 ml was given in 5-ml increments injected every 20 sec. An epidural catheter was then inserted and the patient placed in the supine horizontal position with a wedge under the right hip for left uterine displacement. Blood pressure was then measured every minute for 20 min. Additional local anesthetic was given as necessary through the catheter to achieve a T4-T6 level. Patients were given ephedrine for hy-

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Table 1. Effect of Lidocaine Alkalinization on Blood Pressure^a Responses

	Baseline value (mm Hg)	Minimum value (mm Hg)	Maximum decrease (%)	Average rate of decrease to minimum value (%/min)
Systolic blood pressure				
HCO ₃	137 ± 4	94 ± 5 ^{b,c}	32 ± 3 ^b	9 ± 1 ^b
Control	137 ± 4	111 ± 4	19 ± 3	3 ± 1
Diastolic blood pressure				
HCO ₃	77 ± 1	46 ± 4	39 ± 6	9 ± 3
Control	75 ± 3	51 ± 3	31 ± 5	4 ± 1

^aValues given are mean ± SEM.^b*P* < 0.05 vs control.^c*P* < 0.05 vs baseline.

potension if systolic blood pressure decreased to 80% of baseline value or if systolic pressure decreased below 100 mm Hg.

Blood pressure values before and after anesthetic administration were compared within each treatment group using the paired *t*-test. Differences in corresponding hemodynamic parameters between the two treatment groups were tested for statistical significance by means of unpaired *t*-testing. Differences in amounts of ephedrine and additional lidocaine used in the two groups were analyzed with the Wilcoxon rank sum test and differences in treatment frequencies for these two agents via Fisher's exact test. *P* < 0.05 was considered the criterion for statistical significance.

Results

Baseline systolic and diastolic blood pressures did not differ in the alkalinized and control groups (Table 1). Within each of the treatment groups, both systolic and diastolic blood pressures decreased significantly after administration of anesthetic (column 1 vs column 2). The decreases in systolic blood pressure (SBP) in the alkalinized group were significantly greater than in control patients, with a maximal decrease to 32% below baseline values in the alkalinized group compared with 19% in controls (column 3). The possibility that SBP in the alkalinized group not only decreased to lower minimal values but also declined more rapidly was evaluated by calculating an average rate of SBP decrease, i.e., maximal decrease (in percent of baseline value) divided by the time required to reach that minimal value. The average rate of decrease in SBP (column 4) was three times greater for the alkalinized group than for the controls (9%/min vs 3%/min), a statistically significant difference. Decreases in diastolic blood pressure in the alkalinized group were neither greater nor more rapid than in the control group.

Average SBP levels in the two groups at specific time points are plotted in Figure 1. Significant differences in systolic blood pressure as a percentage of the original baseline were evident at 2, 4, and 6 min but not thereafter. At the 15- and 20-min time points, SBP levels in both groups were returning toward baseline values (data not shown).

Six of ten patients given alkalinized lidocaine received ephedrine, the total dose averaging 21 mg (range 10–55), whereas 3 of 11 control patients received an average total dose of 12 mg ephedrine (range 10–20), a nonsignificant difference. Six of eleven patients in the control group required additional local anesthetic, with an average total dose for the group of 23 ml, as compared to three of ten patients with an average total dose of 21 ml in the alkaline group, differences without statistical significance. There were no technical failures and analgesia was satisfactory in all patients, who remained awake with mild sedation given after delivery of the baby.

Discussion

This small series demonstrates that there are significantly greater magnitudes and rates of decline in systolic blood pressure to minimum levels with alkalinized lidocaine plus epinephrine as compared to regular lidocaine plus epinephrine during epidural anesthesia for cesarean section. This difference became evident at the 2-min time point and persisted through 6 min and cannot be attributed to the more extensive use of local anesthetic or less extensive use of ephedrine in the alkalinized group. This result is not unexpected considering studies cited above showing that onset of epidural analgesia and surgical anesthesia are significantly shortened by the use of the alkalinized solution. The hypotension seen in the alkalinized patients may be analogous to that which occurs during spinal anesthesia, reflecting rapid onset of sympathetic blockade. It should be noted that our study was limited to patients undergoing cesarean section, and

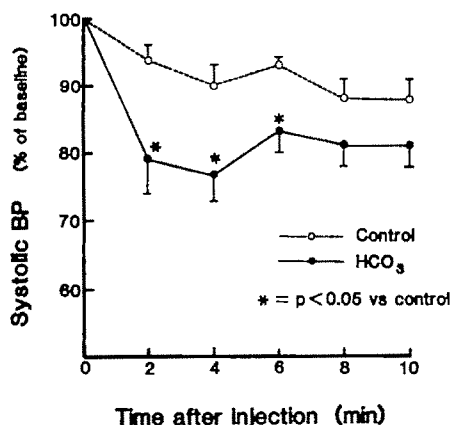


Figure 1. Time course of average systolic blood pressure (BP) readings (mean $\pm$ SEM) expressed as a percentage of the baseline value.

the data may not be applicable to nonpregnant patients having other types of surgery.

The onset of anesthesia and hemodynamic effects with local anesthetic reflects the penetration of the nerve membrane by nonionized local anesthetic. The production of anesthesia is favored by the alkaline pH, through conversion of the ionized (water-soluble) form to the nonionized (lipid-soluble) form. This mechanism has also been invoked in explaining similar effects of carbonated solutions of lidocaine, commercial preparations of which have a near-neutral pH. However, other mechanisms may also be operative in carbonated preparations, including a direct depressant effect of carbon dioxide on neural transmission (2).

Commercial lidocaine plus epinephrine has a pH of 4.5–5.0 to protect epinephrine from the oxidation that would occur with higher levels of pH. The addition of 1 mEq NaHCO₃ to 10 ml lidocaine plus epinephrine increases the pH to 7.0–7.25. The resultant shortened latency period and rapid onset has led others to advocate wider usage of the alkalinized solution (2). We suggest caution, however, in adopting it for cesarean section in view of the significantly greater systolic hypotension demonstrated with the alkalinized preparation in this study. Hypotension during cesarean section with both spinal and epidural anesthesia may be associated with adverse effects on uteroplacental blood flow. This may be especially so in preeclamptic or eclamptic patients because it may further compromise an already decreased uteroplacental circulation (1,6). In the present study, no adverse effects were noted in newborns of either group on the basis of Apgar scores (data not shown), in part perhaps because the present study was not extended beyond the small number of patients sufficient to doc-

ument significantly greater systolic hypotension associated with alkalinization of the epidural local anesthetic solution.

As opposed to the bolus injection used in the present study, injection of repeated, small amounts of alkalinized lidocaine through an epidural catheter might produce less hypotension. Although this would also be expected to negate the benefit of rapid onset, there remains the additional possibility of improved quality of anesthesia with the alkalinized preparation: with carbonated lidocaine, analgesia is less patchy (7,8) and motor block is more intense (3,7). To our knowledge, an improvement in the quality of neural blockade with an alkalinized solution has been demonstrated only in vitro (9); although a better quality of anesthesia has been suggested with bupivacaine, mepivacaine, and lidocaine, only mepivacaine has been studied in a double-blinded fashion (3).

In summary, this study has demonstrated significantly greater systolic hypotension, both in magnitude and in rate of development, during epidural blockade for cesarean section when lidocaine plus epinephrine alkalinized with bicarbonate was used to achieve more rapid onset of anesthesia; we suggest caution in use of this preparation as a bolus injection in such cases.

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The Effect of Ketanserin on Blood Pressure and Platelets during Cardiopulmonary Bypass

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LICHTENTHAL PR, WADE LD, ROSSI EC. The effect of ketanserin on blood pressure and platelets during cardiopulmonary bypass. *Anesth Analg* 1987;66:1151-4.

Ketanserin, a serotonin antagonist, was used to control blood pressure during cardiopulmonary bypass in 12 patients having cardiac surgery. The drug was administered as a 10 mg bolus followed by a continuous infusion of either 40, 80, or 120 mg/hr to maintain mean arterial blood pressure below 70 mm Hg. There were 16 hypertensive episodes of which 15 (93.7%) were successfully controlled with ketanserin. Mean arterial pressure decreased significantly from

an average of 72 ± 3 to 52 ± 9 mm Hg after 1 min. The effect that ketanserin had on platelets was also evaluated. Neither adverse nor salutary effects were seen in the platelet count, though a significant inhibition of serotonin-induced platelet aggregation was observed. Ketanserin proved effective for controlling hypertension during cardiopulmonary bypass but, despite inhibition of serotonin-induced platelet aggregation, it did not prevent thrombocytopenia.

Key Words: PHARMACOLOGY—ketanserin. SEROTONIN—ketanserin. SURGERY—cardiovascular.

Hypertension and thrombocytopenia are common problems associated with cardiopulmonary bypass (CPB) (1,2). Considerable interest has been focused recently on the role that serotonin might play in the production of both hypertension and thrombocytopenia (3,4). Platelet destruction and aggregation releases serotonin into the bloodstream (5). Released serotonin could contribute to hypertension by producing vasoconstriction (6) and to thrombocytopenia by augmenting the aggregating effect of other physiologic agonists of aggregation such as ADP and epinephrine (7). Thus, platelet destruction during CPB could initiate a self-propagating mechanism that could explain both the hypertension and thrombocytopenia often associated with CPB. Ketanserin (KT) is a serotonin antagonist with inhibitory effects on serotonin-induced shape change (8) and aggregation (9) of human platelets that is also effective both orally and intravenously for lowering blood pressure. If platelet destruction does play an important role in the mechanism of hypertension and thrombocytopenia, then KT should prove effective for controlling both of these problems during cardiopulmonary bypass. To test this hypothesis, KT was administered to patients

undergoing hypothermic CPB, and its effect on CPB-induced hypertension and thrombocytopenia was evaluated.

Methods

The study group comprised 12 patients scheduled to undergo elective cardiac surgery for either coronary artery bypass grafting (CABG) or valve replacement. All patients signed an informed consent before participating in this Institutional Review Board approved study. Patients were premedicated with morphine sulfate (0.15 mg/kg) and scopolamine (0.4 mg/70 kg). Anesthesia was induced with diazepam (0.3 mg/kg) and was maintained with and O₂/halothane technique. Pancuronium was used to achieve muscle relaxation. The normal anesthetic and surgical routines were followed until the initiation of cardiopulmonary bypass. After the onset of CPB, the patient's systemic arterial pressure was allowed to stabilize and an optimum flow rate was established by the perfusionist. The flow rate was kept constant for the duration of CPB and was only altered if persistent hypotension developed. After hypothermia was begun and the aorta cross-clamped, hypertension was treated with KT. If the mean arterial pressure (MAP) increased to 70 mm Hg or above, KT was given in a 10-mg bolus dose into the oxygenator of the CPB circuit, followed by an infusion of 40 mg/hr (2 mg/ml) for a minimum of 2 min. The KT infusion was continued as long as MAP

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Table 1. Baseline Patient Data

Number of patients (n)	12
Age (yr)	63.7 ± 9
Sex	Males: 9, females: 3
Weight (kg)	74 ± 13
Heart rate (beats/min)	66.7 ± 3.8
Systolic pressure (mm Hg)	138.5 ± 25.1
Cardiac output (L/min)	5.69 ± 1.04 ^a

Values expressed as mean ± SD.

^aNumber of patients = 8.

remained between 45 and 70 mm Hg. If the MAP remained elevated or returned to levels above 70 mm Hg, another 10-mg bolus of KT was given, followed immediately by a KT infusion at 80 mg/hr. This KT administration schedule was followed, up to a maximum of three bolus doses and an infusion of 120 mg/hr. If the maximal dose of KT did not maintain MAP below 70 mm Hg, then KT was considered a failure and sodium nitroprusside (SNP) was given by slow infusion into the oxygenator, to lower the patient's pressure. On the other hand, if the MAP decreased below 45 mm Hg for longer than 1 min the KT infusion was stopped. Ketanserin was considered to have successfully controlled hypertension if SNP did not have to be used. During CPB, hemodynamic measurements were recorded every 15 min or with a change in dose of KT. The *t*-test for paired data was used for the statistical analysis of hemodynamic data.

To document an effect of KT on serotonin-induced platelet aggregation, a baseline blood sample for aggregation studies was drawn after surgical preparation for CPB but before infusion of KT (pre-CPB). A second sample was drawn 1 hr after application of the aortic cross-clamp (during or within 45 min of KT infusion), and a third sample was drawn 1 hr after application of the aortic cross-clamp. Blood mixed with 3.8 gm/dl trisodium citrate (9:1 ratio by volume) was centrifuged at 150 × *g* for 10 min. Platelet-rich plasma (PRP) was removed and the residual blood was centrifuged at 2000 × *g* for 5 min to produce platelet-poor plasma. Platelet aggregation studies were performed as described previously (10). Light transmission (LT) values of PRP and PPP were defined as zero and 100% aggregation respectively, and the zero PRP baseline was adjusted, as necessary, to maintain the same 0–100% scale of aggregation.

Platelet aggregation was initiated by addition of one of three aggregants in amounts adequate to produce the final concentrations indicated: serotonin (5 μM); epinephrine (4 μM); or ADP (1.5 μM). Percent aggregation 1 min after addition of aggregant was recorded. Results were expressed as the percent inhibition of pre-CPB aggregation values observed 1 hr

Table 2. Mean Arterial Pressure and Systemic Vascular Resistance before and after a 10-mg Bolus of Ketanserin (KT)

	Before KT	After KT
Systemic pressure (mm Hg)	72.3 ± 3.0	50.7 ± 10.7 ^a
Systemic vascular resistance (dynes-sec-cm ⁻⁵)	1378 ± 141	914 ± 172 ^b

Results are expressed as mean ± SD.

^a*P* < 0.001.^b*P* < 0.05.

after cross-clamping and 24 hr postoperatively (i.e., during and after KT infusion, respectively), and they were calculated according to the following formula:

$$\% \text{ Inhibition} = 100 - \frac{\text{percent aggregation during cross-clamping} \times 100}{\text{percent aggregation pre-CPB}}$$

This calculation corrects for variable hematocrits and platelets counts, and permits a comparison of the effects of KT on serotonin, epinephrine, and ADP-induced platelet aggregation. Statistical analysis was accomplished by the Kruskal-Wallis test, a nonparametric alternative to the analysis of variance (11).

Results

Pertinent physical data characterizing the patients who participated in the study are presented in Table 1. Ketanserin successfully controlled hypertension during CPB in 11 of the 12 patients (91.9%). A total of 16 hypertensive events occurred, of which 15 (93.75%) were successfully treated with KT. The single hypertensive event that the maximal dose of KT was unable to control was the only event that occurred in that patient, and was successfully treated with SNP. A 10-mg bolus of KT caused a maximal lowering of blood pressure from a mean of 72.3 ± 3.0 to 50.7 ± 10.7 mm Hg (*P* < 0.001) within 2 min (includes data from failed event, Table 2). Peak effect of KT on blood pressure was usually observed within 1 min, at which point the average mean pressure had decreased more than 20 mm Hg to 51.6 ± 9.44 mm Hg (*P* < 0.001). Systemic vascular resistance also decreased significantly with KT administration, 1378 ± 141 before to 914 ± 172 dynes-sec-cm⁻⁵ after KT (*P* < 0.05). The infusion rates required to keep MAP below 70 mm Hg for each of the 16 events is depicted in Figure 1. An infusion of KT at 40 mg/hr proved to be an adequate initial rate. Figure 2 illustrates the average mean pressures that were maintained by an infusion of KT at 40 mg/hr for the first 15 min of treatment (most of the hypertensive events did not last much longer than 15 min). The cumulative dose of KT given for each

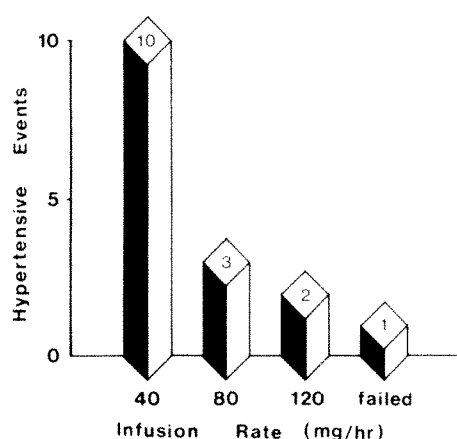


Figure 1. Infusion rates of ketanserin required to maintain MAP below 70 mm Hg.

successfully treated hypertensive event varied greatly, ranging from 160 to 1558 $\mu\text{g/kg}$, with a mean dose of $466.5 \pm 343 \mu\text{g/kg}$.

Although KT effectively controlled blood pressure, an effect on the platelet count was not demonstrated. After institution of CPB and treatment with KT, the platelet counts in whole blood decreased from an average of $237,000 \pm 50,000$ to $96,000 \pm 35,000$ platelets/cu mm ($P < 0.001$), whereas hematocrit values declined from 30 ± 3 to $19 \pm 3\%$ ($P < 0.001$). Twenty-four hours postoperatively the hematocrit averaged $27 \pm 3\%$, but the platelet count remained low postoperatively, at $90,000 \pm 31,000$ platelets/cu mm. Although KT did not prevent thrombocytopenia, it did inhibit serotonin-induced platelet aggregation. During or within 45 min of KT infusion, the percent inhibition of serotonin-induced platelet aggregation was $64 \pm 19\%$, compared with $29 \pm 26\%$ for epinephrine and $17 \pm 22\%$ for ADP-induced platelet aggregation ($P < 0.01$). After clearance of KT (24 hr postoperatively) platelets were again responsive to serotonin, and differences between serotonin-, epinephrine-, and ADP-induced aggregation were no longer present.

Discussion

Cardiopulmonary bypass resulted in a 37% decline in hematocrit and a 60% decline in platelet count. This agrees closely with the study of Mammen et al. (12), which reported a 34% decline in hematocrit and a 53% decline in platelet count. In our study, the disproportionate decline in platelets was not modified by KT, despite its demonstrable inhibitory effect on serotonin-induced platelet aggregation. Mammen et al. (12) and Harker et al. (13) have shown that CPB is also associated with defects in platelet aggregation. Our

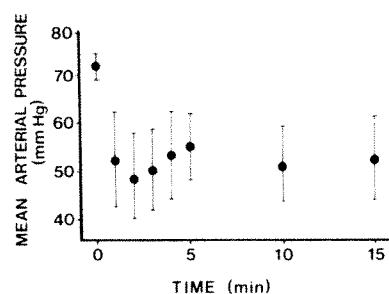


Figure 2. Average MAP observed after administration of ketanserin as a 10-mg bolus followed by a continuous infusion at 40 mg/hr.

study confirmed this and also showed a selectively greater inhibition of serotonin-induced aggregation associated with KT infusion. Despite this apparent effect on serotonin-induced platelet aggregation, KT did not protect platelets during CPB. This suggests that release of serotonin from platelets does not significantly contribute to the thrombocytopenia observed during CPB.

Ketanserin was clearly an effective antihypertensive agent with a $>90\%$ success rate during hypothermic CPB. The decrease in mean arterial blood pressure was due to vasodilation of constricted vessels as indicated by the significant reduction in systemic vascular resistance. Bolus administration of the drug lowered blood pressure not only significantly but, more importantly, to a clinically desirable level. Furthermore, this response was seen almost immediately after the drug was given. Ketanserin infusions of 40–80 mg/hr were usually adequate for maintaining normotension.

Ketanserin is an α -1-adrenergic inhibitor as well as a serotonin antagonist. As a result, there is some controversy concerning the primary mechanism by which KT lowers blood pressure (14,15,16). Our study does not address this question. However, our data do demonstrate that, regardless of its mechanism of action, KT is an effective drug for controlling hypertension during CPB. This experiment, and others by Van der Starre et al. (17,18) using KT to successfully control blood pressure postoperatively in patients after open heart surgery, indicate that further clinical studies on this novel antihypertensive drug are warranted.

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Nalbuphine as an Analgesic Component in Balanced Anesthesia for Cardiac Surgery

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ZSIGMOND EK, WINNIE AP, RAZA SMA, WANG XY, BARABAS E. Nalbuphine as an analgesic component in balanced anesthesia for cardiac surgery. *Anesth Analg* 1987;66:1155-64.

The efficacy and safety of nalbuphine hydrochloride as an IV analgesic used in combination with pretreatment and supplemental doses of diazepam with and without N₂O were assessed in 15 patients scheduled to undergo aortocoronary bypass (n = 11) or valve replacement surgery (n = 4). The loading infusion of 3.0 mg/kg nalbuphine given in 20 min 5 min after conclusion of IV injection of 0.4 mg/kg/5 min diazepam caused no significant changes in systolic or diastolic systemic and pulmonary arterial blood pressures or in heart rate, cardiac index, stroke index, systemic and pulmonary vascular resistance, or right and left ventricular

stroke work index. After the initial 1-hr loading infusion of 6.66 ± 0.89 mg/kg nalbuphine (mean $\pm$ SE), additional nalbuphine infusion maintenance doses of 4.73 ± 0.77 , 1.87 ± 0.31 , 2.16 ± 0.23 , 1.65 ± 0.22 , and 2.35 ± 0.44 were used in the subsequent hourly periods to maintain a pain-free state throughout surgery. Hemodynamic changes during the three most stressful periods, tracheal intubation, skin incision, and sternotomy, were not statistically significant. Normal plasma catecholamine and cortisol levels indicate that these patients experienced neither stress nor pain during the maintenance of anesthesia. Nalbuphine caused no significant histamine release. All patients had uncomplicated maintenance of and emergence from anesthesia.

Key Words: ANALGESICS—nalbuphine. ANESTHESIA—cardiovascular.

Combining droperidol with fentanyl has proved to be an effective and safe anesthetic technique in balanced anesthesia for cardiac surgery (1,2). However, hypotension (3), bradycardia (4), intraoperative chest wall rigidity (5), prolonged postoperative respiratory depression (6), and intraoperative awareness of events and pain (7) associated with use of fentanyl for this purpose have led to a continued search for safer and more reliable analgesic agents. Two properties of the much less potent analgesic agonist-antagonist, nalbuphine, namely, lack of cardiac depression (8) and a ceiling effect on respiratory depression (9), make it appear to be potentially suitable as an analgesic component in balanced anesthesia if it possesses sufficient analgesic potency for cardiac surgery. Lake et al. (10) corroborated the lack of cardiovascular depression or

other adverse side effects with nalbuphine but found that it lacked sufficient analgesic potency as the sole analgesic agent. Nalbuphine does, however, reduce the mean alveolar concentration of inhalation anesthetics (11). Therefore, we combined it with N₂O:O₂ 50%:50% after pretreatment with diazepam, based on our earlier observation that diazepam reduced the sympathetic stimulation induced by ketamine and/or tracheal intubation (12).

In the present study, we measured diazepam and nalbuphine dose requirements and nalbuphine blood levels in patients undergoing cardiac surgery. Hemodynamic data were also determined, as were plasma catecholamine and cortisol concentrations before and after the use of each agent. Additional hemodynamic and laboratory determinations were recorded throughout cardiac surgery, especially at critical time periods when sympathetic central and adrenomedullary stimulation is maximal; i.e., after tracheal intubation, skin incision, and sternotomy. Because lack of histamine release is a major advantage of an analgesic selected for cardiac anesthesia (13), we also measured plasma histamine concentrations to substantiate in humans the low histamine-releasing potential of nalbuphine reported in animals.

A preliminary report was presented in part at the 8th World Congress of Anesthesiologists, Manila, Philippines, January 22-27, 1984. *Proc. World Congress. Anesth.*, Abstracts, p. A335, 1984.

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Materials and Methods

Study Design

The original study was a randomized double-blind comparison of 20 patients each of whom received either fentanyl or nalbuphine in a slow intravenous infusion for 20 min after the intravenous administration of diazepam. Despite the slow infusion rate of fentanyl ($2.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), severe chest wall rigidity developed in four patients; therefore, the double-blind design was abandoned and the rest of the study was conducted as an open study. Five additional patients were excluded from statistical analysis because of deviations from the protocol. None of these patients developed any adverse effects.

Population Description

Fifteen patients with a mean ejection fraction (EF) of 0.54 ± 0.06 (range 0.20–0.76) who were scheduled to undergo elective cardiac surgery were studied; 11 patients were scheduled for coronary artery bypass and 4 for valve replacement. Each gave written consent as required by the Institutional Research Review Board. There were ten male and five female patients: ten whites, four blacks, and one Spanish American. The mean age was 58.9 years (range 29–74); mean weight, 76.4 kg (range 55–102); mean body surface area, 1.89 m^2 (range 1.54–2.19), and ASA physical status averaged 3.7 (range II–IV). Oral propranolol and oral digitalis doses were discontinued the night before surgery. No patients in physical status V were studied. No patients were being treated with long-lasting β -blockers or calcium-channel blockers, which had not been introduced into clinical practice at the time of our study.

Study Methodology

In the evening before surgery each patient received 1.0 mg/kg IM hydroxyzine hydrochloride at 9:00 PM to allay anxiety and allow a good night's sleep. For preoperative medication, each patient received 2.0 mg/kg IM hydroxyzine hydrochloride at 6:00 AM or on awakening. Eleven patients undergoing coronary bypass surgery (CABG) and 1 patient undergoing mitral valve replacement and CABG received no anticholinergic; 2 patients undergoing valve replacement and 1 patient undergoing repair of atrial septal defect received $3.0 \mu\text{g}/\text{kg}$ glycopyrrolate IM.

Monitoring

In the preoperative preparation area, three intravenous lines were placed into upper extremity veins; an

arterial plastic catheter was introduced into a radial or brachial artery under local anesthesia; a balloon-tipped pulmonary artery catheter was inserted through an internal jugular vein. ECG and noninvasive blood pressure (Dinamap) monitoring were continued in the preoperative preparation area until the patients were transferred to the operating room. Direct arterial systemic pressure, pulmonary artery pressure, and ECG were recorded on a multichannel monitor linked to a computer terminal. Exhaled CO_2 tension was displayed continually and was recorded by a capnograph to assure maintenance of normal alveolar CO_2 levels. Arterial oxygen saturation was continuously measured by transcutaneous infrared oxymeter. Ventilatory rate and tidal volume were recorded by a spirometer. Blood gas tensions were determined at each blood sampling and whenever needed. Cardiac output was determined by thermodilution with a cardiac output computer in triplicate.

Hemodynamic data were determined and collected at the following times before and throughout anesthesia and surgery:

1. Before IV diazepam administration: preinduction.
2. Before nalbuphine IV infusion or 10 min after the start of diazepam IV injection: prenalbuphine.
3. Before pancuronium but at the end of 20-min nalbuphine infusion: postnalbuphine.
4. Before tracheal intubation and 5 min after pancuronium: preintubation.
5. Five minutes after intubation but before surgical incision: postintubation.
6. Immediately before surgical incision: preincision.
7. Fifteen minutes after surgical incision: postincision.
8. Immediately before sternotomy: presternotomy.
9. Ten minutes after sternotomy: poststernotomy.
10. Immediately before the start of cardiopulmonary bypass: prebypass.
11. Ten minutes after the termination of cardiopulmonary bypass: postbypass.
12. At the end of surgical procedure.

Hemodynamic parameters evaluated were:

Heart rate (HR).

Systolic systemic blood pressure: (P_s) mm Hg.

Diastolic systemic blood pressure: (P_d) mm Hg.

Pulmonary artery systolic blood pressure: (P_{a_s}) mm Hg.

Pulmonary artery diastolic blood pressure: (P_{a_d}) mm Hg.

Pulmonary artery wedge pressure: (P_{a_w}) mm Hg.

Central venous pressure (CVP): $\text{cm H}_2\text{O}$.

Table 1. Change in Measured Hemodynamic Parameters before and during Anesthesia^a

Time	Heart rate	Arterial blood pressure		Pulmonary arterial blood pressure		Cardiac	
		Systolic	Diastolic	Systolic	Diastolic	Output	Index
Preinduction	72.5	140.7	61.9	28.1	8.7	7.10	3.67
	± 4.4	5.7	3.7	2.7	1.9	0.73	0.33
Prenalbuphine	0.1	-23.1 ^b	-7.4 ^b	1.1	0.9	-0.88	-0.43
	± 2.9	5.8	3.0	3.6	1.6	0.47	0.23
Postnalbuphine	1.4	-25.4 ^b	-5.4	0.5	2.5	-0.52	-0.26
	± 2.9	5.8	3.1	3.3	1.7	0.59	0.30
Preintubation	8.7	-20.0 ^b	-3.2	-2.5	1.6	-1.02	-0.48
	± 4.0	8.1	6.0	3.0	1.7	0.75	0.37
Postintubation	27.5 ^b	-12.04	0.2	-1.5	3.0	-1.0	-0.5
	± 8.9	6.9	4.8	3.5	2.4	0.51	0.24
Preincision	27.5 ^b	-12.0	0.3	-1.4	3.5	-1.88 ^b	-0.94 ^b
	± 9.2	8.0	4.8	3.4	2.2	0.70	0.34
Postincision	10.6 ^b	-6.9	8.3 ^b	-1.3	4.3	-1.40	-0.74 ^b
	± 4.7	7.0	2.9	5.1	3.2	0.54	0.27
Presternotomy	0.7	-9.7	4.0	-2.5	4.8	-1.36	-0.71
	± 3.4	7.2	5.3	3.7	2.5	0.65	0.33
Poststernotomy	8.1	-17.9 ^b	3.4	-4.0	0.9	-1.69 ^b	-0.86
	± 4.7	6.1	4.1	2.7	2.1	0.79	0.39

^aValues are means ± SE.^bP < 0.05.

Cardiac output (CO): L/min.

The following hemodynamic data were calculated:

Cardiac index (CI): L/min/m².

Stroke volume (SV): ml.

Stroke index (SI): ml/m².Systemic vascular resistance (SVR): dynes·sec·cm⁻⁵.Pulmonary vascular resistance (PVR): dynes·sec·cm⁻⁵.Left ventricular stroke work index (LVSWI): gram-meter/m².Right ventricular stroke work index (RVSWI): gram-meter/m².

Anesthetic Management

For induction of tranquilization/hypnosis, 0.4 mg/kg diazepam was given IV over 5 min with 100% O₂ with spontaneous ventilation. After an additional 5-min interval, the IV infusion of 3.0 mg/kg nalbuphine was begun and continued for 20 min. At the termination of nalbuphine infusion, 0.1 mg/kg IV pancuronium bromide was given. Five minutes after injection of pancuronium, tracheal intubation was carried out without spraying of local anesthetic solution. After confirming the correct position of the endotracheal tube, 50% N₂O in oxygen was administered. None of the patients received N₂O before the completion of hemodynamic and hormone level determinations fol-

lowing intubation. Additional doses of nalbuphine were given in 0.25 mg/kg IV incremental doses based on the following criteria: 1) pupil diameter > 2.0 mm bilaterally; 2) increase in rate pressure product greater than 20%; 3) other clinical evidence of inadequate pain relief, including lacrimation, sweating, decrease in finger pulse recording, and rapid eye movements. The sums of the doses for each 30-min period were recorded and the means determined. Additional doses of diazepam were given when eye signs and autonomic and hemodynamic changes indicated light levels of anesthesia. Additional doses of pancuronium were given throughout anesthesia based on the response to ulnar nerve stimulation. No patient received IV vasopressors and/or vasodilator drugs until cardiopulmonary bypass. Although data were collected throughout anesthesia before and after cardiopulmonary bypass, the results are not presented after bypass, because many other factors besides the anesthesia influenced postbypass findings.

During the postoperative period, the following were recorded: the investigator's evaluation of the procedure based on the review of complications, such as episodes of arrhythmias, brady- or tachycardia, hypo- or hypertension, bronchospasm, hypersecretions on induction, and maintenance (excellent, good, fair, poor); times to recovery of spontaneous respiration, wakefulness, and to the first analgesic administration; and degree of analgesia (excellent, good, fair, poor) and amnesia (none, some, or total).

Table 2. Changes in Calculated Hemodynamic Parameters before and during Anesthesia

Time	Stroke		Vascular resistance		LVSWI	RVSWI
	Volume	Index	Systemic	Pulmonary		
Preinduction	103.0	53.3	1077.6	82.3	66.74	10.16
	9.5	4.4	115.9	10.4	5.99	1.52
Prenalbuphine	-9.0	-4.6	-136.0	27.4	-14.57 ^a	0.96
	4.7	2.3	102.3	27.3	3.91	1.17
Postnalbuphine	-9.5	-5.3	-227.4	8.8	-16.12	1.98
	8.5	4.2	140.9	15.5	5.55	1.86
Preintubation	-21.6	-10.7	-80.5	21.5	-18.69 ^a	-0.03
	9.4	4.6	138.3	12.8	5.42	1.24
Postintubation	-21.0	-10.7	-47.4	15.2	-17.09 ^a	0.0
	7.1	3.5	134.9	7.9	4.75	1.47
Preincision	-41.3 ^a	21.1	-15.3	30.9	-17.09	0.0
	9.5	4.6	143.6	12.8	4.75	1.47
Postincision	-42.5 ^a	-21.1 ^a	296.9 ^a	-11.2	-18.96	-2.58
	9.1	4.6	66.9	22.9	6.20	2.71
Presternotomy	-19.4 ^a	-10.0 ^a	109.2	-18.0	-14.87	-0.04
	8.5	4.4	198.9	14.2	4.48	1.03
Poststernotomy	-31.6 ^a	-16.1 ^a	101.8	34.5	-16.74 ^a	-1.22
	10.1	5.1	118.5	19.8	4.83	1.25

^a $P < 0.05$.

Laboratory Determinations

Plasma catecholamine levels were determined in fresh-frozen plasma separated by cold centrifugation of blood samples taken into ice-cold heparinized tubes from the arterial line. Plasma catecholamines (norepinephrine, epinephrine, and dopamine) were determined by high-pressure liquid chromatography (14,15) at times of maximal stress when hemodynamic changes were anticipated. Plasma cortisol concentrations were determined by a radioimmunoassay (16). Histamine concentrations were analyzed by a fluorometric assay technique (17). The normal ranges, the limits of detection, and coefficients of variation for each assay were as follows: Ranges of normal values for norepinephrine, epinephrine, and dopamine in the supine position were: 110–410, <50, and <50 pg/ml, respectively; for cortisol and histamine: 7–27 and 0–15 μ g/dl, respectively. The limits of detection were: 15 pg/ml for norepinephrine, 15 pg/ml for epinephrine, 20 pg/ml for dopamine, 2 μ g/dl for cortisol, and 10 ng/ml for histamine. The coefficients of variations were 12.7, 10.3, 14.1, 5.0 and 22%, respectively.

Statistical Methodology

The hemodynamic parameters and plasma hormone levels were evaluated for the change from baseline at each sampling time during the procedure, using the paired *t*-test. Baseline was defined in two ways: as preinduction and as prenalbuphine. The hemodynamic parameters and plasma catecholamine levels were also evaluated for the changes due to intubation, surgical incision, and sternotomy, using a paired *t*-

test based on change from the preevent value to postevent value. All statistical tests were two-tailed and statistical significance was defined at $P \leq 0.05$. All values are expressed as mean $\pm$ SE (standard error of the mean) throughout the text.

Results

Hemodynamic Changes

Intravenous injection of diazepam significantly decreased systolic arterial and diastolic pressures ($P \leq 0.05$), but without concomitant changes in other directly measured or calculated hemodynamic parameters (Tables 1 and 2; Fig. 1–4).

Intravenous infusion of 3.0 mg/kg nalbuphine for 20 min caused no significant changes in hemodynamics (Tables 1 and 2; Fig. 1–4).

Changes in hemodynamic parameters caused by tracheal intubation are shown in Figures 1–4. Heart rate did not change significantly, nor did systemic and pulmonary arterial pressures. Cardiac output and CI decreased, but SV, SI, SVR, and PVR were not significantly altered by intubation.

The changes in hemodynamic parameters caused by surgical incision are shown in Figures 1–4. No changes in any of the observed hemodynamic parameters reached statistical significance.

The changes in hemodynamic parameters after sternotomy are shown in Figures 1–4. The only statistically significant change observed after sternotomy was a reduction in pulmonary artery diastolic pressure.

In summary, intubation, surgical incision, and ster-

Figure 1. Changes in systolic and diastolic systemic blood pressures, heart rate, and pulmonary arterial pressures during balanced anesthesia with nalbuphine as an analgesic. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

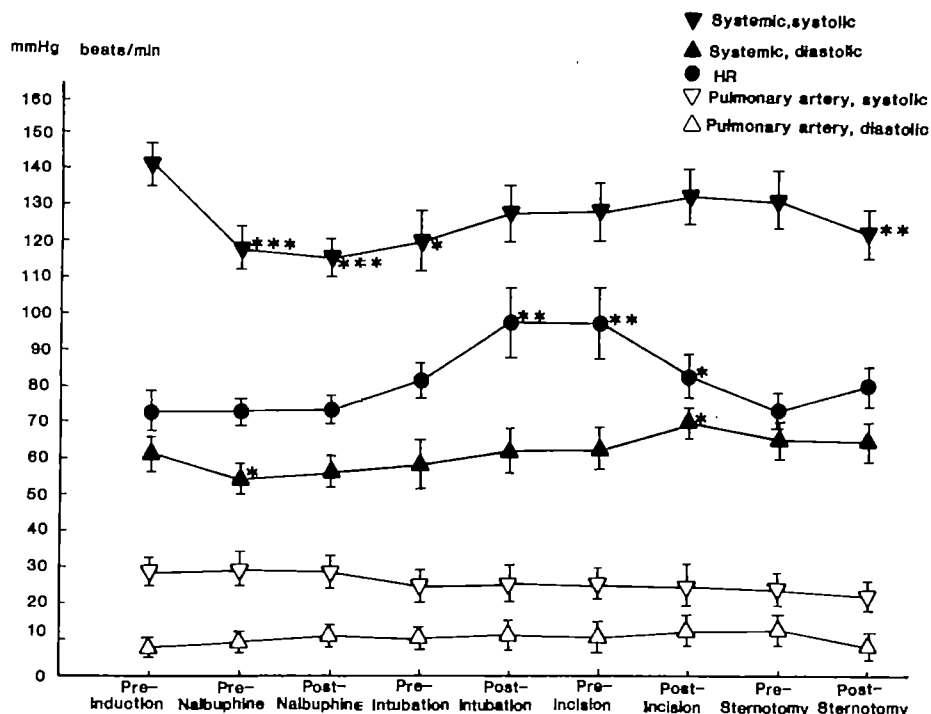
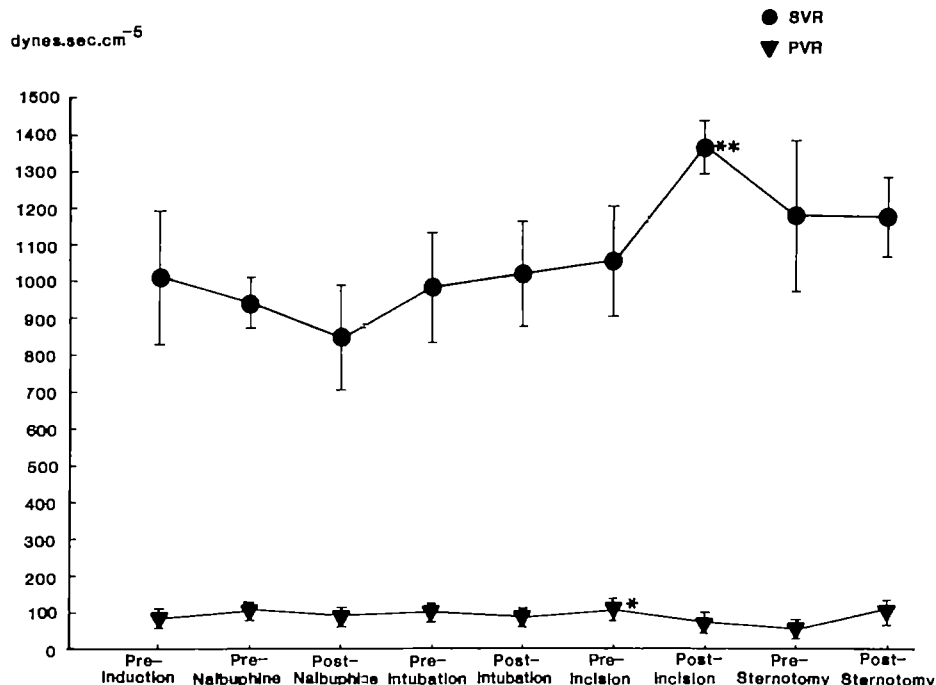


Figure 2. Changes in systemic and pulmonary vascular resistances during balanced anesthesia with nalbuphine as an analgesic. * $P < 0.05$, ** $P < 0.01$.



notomy caused only moderate or no adverse hemodynamic changes.

Catecholamine Plasma Levels

Induction of anesthesia with diazepam caused a significant reduction in plasma epinephrine concentration (Fig. 5).

The infusion of 3.0 mg/kg nalbuphine for 20 min caused no significant changes in norepinephrine, epinephrine, and dopamine concentrations (Fig. 5).

Surgical incision and tracheal intubation caused no significant changes in catecholamine levels, whereas sternotomy caused a significant increase in plasma epinephrine but not in norepinephrine or dopamine levels (Fig. 5).

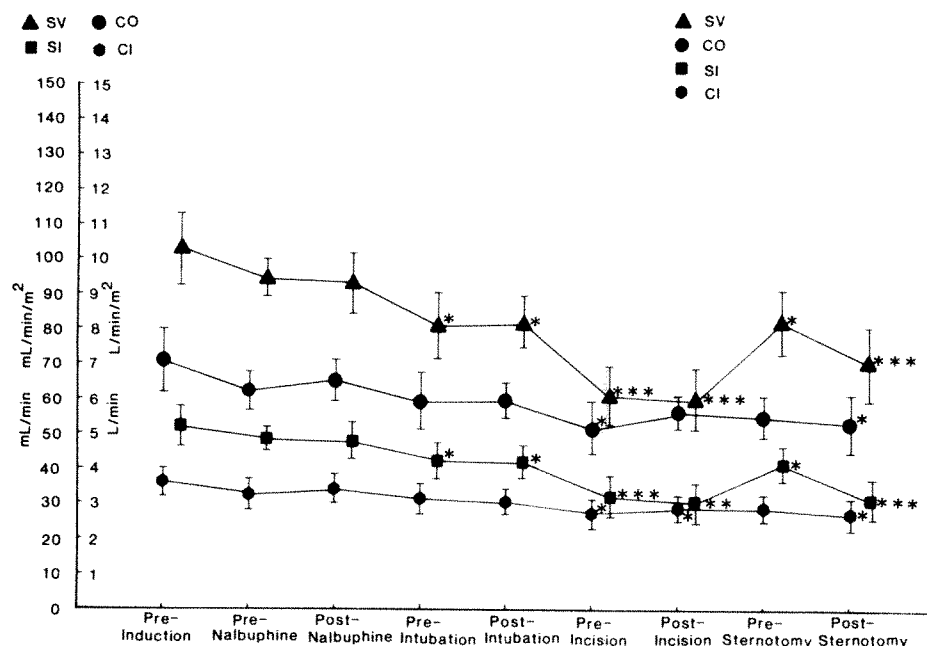


Figure 3. Changes in cardiac output and index and in stroke volume and stroke volume index during balanced anesthesia with nalbuphine as an analgesic. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

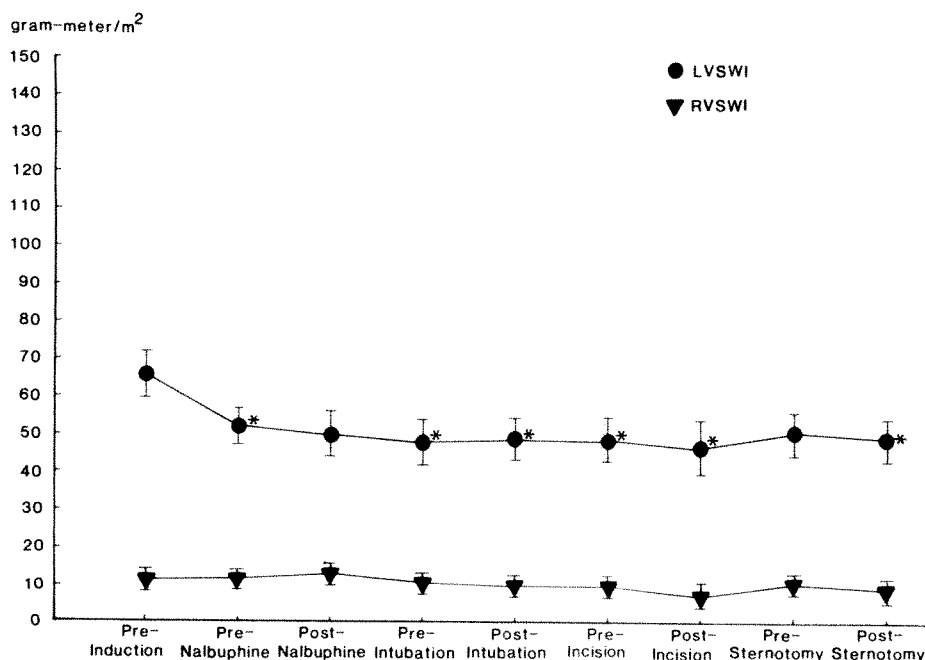


Figure 4. Changes in left and right ventricular stroke work indexes during balanced anesthesia with nalbuphine as an analgesic. * $P < 0.05$.

Cortisol Plasma Levels

No significant alterations in cortisol levels were observed at any time during anesthesia and surgery (Fig. 6).

Histamine Plasma Levels

No significant increases in histamine levels were noted throughout anesthesia and surgery (Fig. 6).

Evaluation of the Efficacy of Anesthesia and Analgesia

Induction of anesthesia was rated as good in 2 patients (13%) and excellent in 13 patients (87%). Maintenance was rated as excellent in all patients (100%), because no bradycardia, tachycardia, arrhythmias, hypotension, or hypertension occurred from induction to cardiopulmonary bypass. Postoperative analgesia was rated as excellent in 12 of 15 patients (80%). No patient

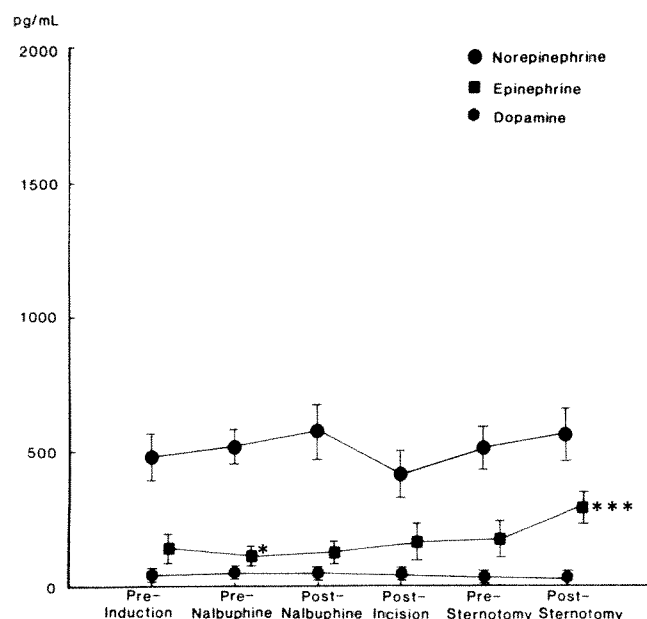


Figure 5. Changes in plasma norepinephrine, epinephrine, and dopamine concentrations during balanced anesthesia with nalbuphine as an analgesic. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

had recall of pain or any events during anesthesia and surgery (100% total amnesia).

Recovery from Anesthesia

The duration of anesthesia averaged 10.5 ± 0.54 hr (range 7.5–14.7). The time from the end of anesthesia to recovery of wakefulness averaged 7.3 ± 1.0 hr (range 1.8–14.5). The time from the end of anesthesia to spontaneous respiration averaged 7.3 ± 1.4 hr (range 0.5–17.0). The time between the end of anesthesia and the first required analgesic dose averaged 14.8 ± 6.6 hr.

Dose Requirements

Nalbuphine dose requirements are shown in Figure 7. The total dose of nalbuphine averaged 17.2 ± 1.46 mg/kg. The initial loading dose was 6.66 ± 0.89 mg/kg for the first hour; maintenance doses were 4.73 ± 0.77 , 1.87 ± 0.31 , 2.16 ± 0.23 , 1.65 ± 0.22 , and 2.35 ± 0.44 mg/kg for the subsequent hourly periods. Diazepam total dose requirement was 0.77 ± 0.05 mg/kg for the duration of anesthesia; an additional dose of 0.37 ± 0.05 mg/kg was given after the initial dose of 0.4 mg/kg. The hourly dose requirement of diazepam was $0.9 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. After the initial 0.1 mg/kg pancuronium, additional doses of pancuronium totaling 0.15 ± 0.02 mg/kg or $0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ were needed throughout the procedure.

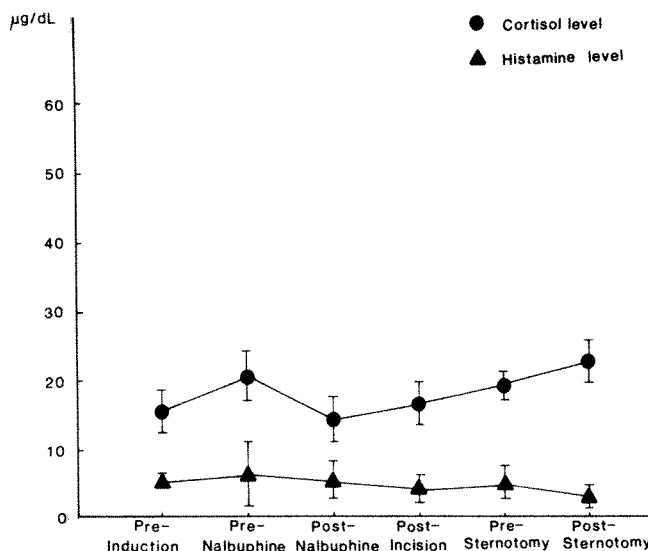


Figure 6. Changes in plasma cortisol and histamine concentrations during balanced anesthesia with nalbuphine as an analgesic.

Discussion

This is the first report on the successful use of nalbuphine as the analgesic component of diazepam-nalbuphine- N_2O -pancuronium-balanced anesthesia for induction and maintenance in cardiac patients undergoing coronary artery bypass surgery and/or valvular surgery. We emphasize that IV pretreatment with diazepam before IV nalbuphine infusion also contributed to the adequacy of anesthesia, because Lake et al. (10) were unable to provide adequate anesthetic conditions with the IV infusion of 3.0 mg/kg nalbuphine alone in cardiac surgical patients. The latter authors intended to provide complete anesthesia with nalbuphine alone and hence employed no IV diazepam pretreatment. This methodologic difference may explain the seeming discrepancy between their and our results. The use of pancuronium for tracheal intubation and for the maintenance of muscle relaxation in our patients further contributed to the hemodynamic and endocrine stability. We selected pancuronium, because we earlier observed no hemodynamic changes after its use for tracheal intubation in cardiac surgical patients in whom anesthesia was induced with diazepam-ketamine (18).

We did not intend to use nalbuphine alone as an "anesthetic" agent to provide analgesia, amnesia, endocrine and hemodynamic protection from "stress" but, rather, as an analgesic component of balanced anesthesia. Therefore, our study neither addressed nor answered the question whether nalbuphine alone, even in high doses, could provide adequate analgesia, amnesia and hemodynamic stability throughout the

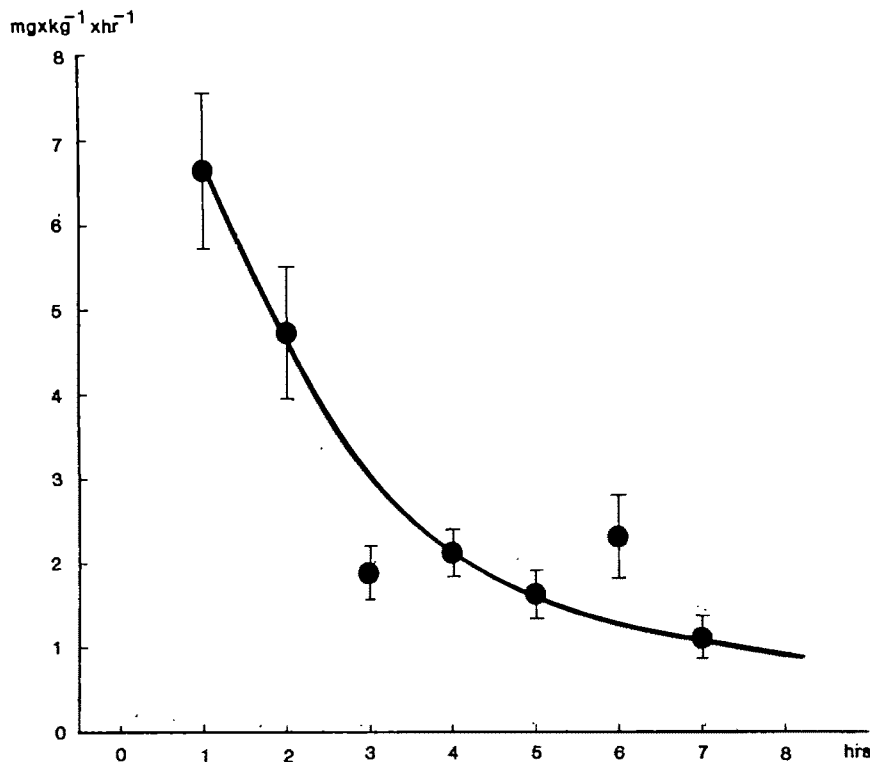


Figure 7. Nalbuphine dose requirements for balanced anesthesia with nalbuphine as an analgesic.

conduct of cardiac surgery. The same hemodynamic stability as we observed in this study can be achieved only by the administration of very high doses of fentanyl in the absence of pretreatment and supplementation with diazepam or inhalational agents (19,20). Furthermore, our findings also demonstrated that even a narcotic-analgesic with low potency such as nalbuphine with 80% of the potency of morphine (21) can, in combination with diazepam pretreatment, provide sufficient and safe anesthesia for cardiac surgery, contrary to claims that solely analgesics with high potency are effective and safe as a component of neuroleptanalgesia (22,23). In spite of the high total milligram per kilogram dose of nalbuphine, no adverse effects, such as bradycardia, hypotension, chest wall rigidity, increase in catecholamines reported after the use of medium, and high doses of fentanyl without other supplementing agents, were observed in our patients (4,5,19,20).

Our study proved the efficacy of nalbuphine as an analgesic component in combination with diazepam for induction or diazepam with 50% N₂O:O₂ for maintenance. It is well accepted that pain causes marked increase in sympathetic activity. Because no significant increases in systolic or diastolic blood pressures (Fig. 1) or in plasma-free norepinephrine (Fig. 5) concentrations were observed after intubation, skin incision, and sternotomy, no stress responses to painful

stimulation were evident in our patients. Nor was there any recall of painful events throughout the procedure based on the postoperative interview. All patients were willing to accept our anesthetic technique for surgery if required in the future.

The safety of nalbuphine as an analgesic component of diazepam-nalbuphine-balanced anesthesia for induction is confirmed by the lack of significant hemodynamic changes (Fig. 1-4) after the IV infusion of 3.0 mg/kg nalbuphine over 20 min. This finding corroborates the earlier reports of Lake et al. (10). Nalbuphine did not increase pulmonary artery systolic, mean diastolic, or wedge pressures, in contrast to the findings of Popio et al. (24) with butorphanol.

The safety of nalbuphine, even when utilized in large intravenous doses, is further documented by a lack of histamine release during intravenous infusion (Fig. 6). Morphine, in contrast, causes histamine release (13), an adverse circulatory effect that may not be tolerated by cardiac patients. Chest wall rigidity was not observed in any of our patients anesthetized with the technique described in the present study. On the contrary, none of the four patients in our original double-blind study tolerated completion of the IV infusion of 40 µg/kg fentanyl in 20 min because of the development of chest wall rigidity, and all required prompt tracheal intubation. For that reason, our study was changed to an open-label study. In

contrast to fentanyl, the induction doses of nalbuphine may be titrated up to the required analgesic loading dose without the prior use of a muscle relaxant (22,25).

Diazepam alone before nalbuphine infusion significantly decreased systolic and diastolic systemic pressures and plasma epinephrine levels without significant reductions in CO, CI, SV, SI, SVR, and PVR (Fig. 1-5). LVSWI was reduced, which reflects a marked reduction in cardiac work load (Fig. 4).

The loading or maintenance doses of nalbuphine caused no adverse cardiovascular changes such as bradycardia, tachycardia, arrhythmias, hypertension, hypotension, and decreases or increases in SVR. The sustained reduction in LVSWI from induction to cardiopulmonary bypass (Fig. 4) indicated reduced left ventricular work load. Nalbuphine infusion alone caused no change in catecholamine levels, a potential advantage in cardiac patients (Fig. 5). Analysis of catecholamine and hemodynamic changes associated with intubation further reassures one that the 3.3-mg/kg nalbuphine infusion after 0.4 mg/kg diazepam was sufficient to prevent excessive autonomic activity, as previously observed with diazepam-ketamine (12). Similarly, skin incision elicited no increase in catecholamine levels or in sympathetic activity (Fig. 5). Comparison of the catecholamine levels before and after sternotomy indicated no significant changes in norepinephrine or epinephrine level after sternotomy, although the increase in epinephrine reached statistical significance when compared with the preinduction level. The lack of a significant increase in cortisol levels shown in Fig. 6 with reduced pulmonary artery diastolic pressure and SVR after sternotomy emphasize the autonomic, endocrine, and hemodynamic stability with this anesthetic sequence. Hence, nalbuphine in combination with diazepam pretreatment appears to be a safe alternative balanced anesthetic technique for cardiac patients treated with short-acting β -blockers such as propranolol with ejection fraction ranging from 0.2 to 0.7. However, our favorable hemodynamic and endocrine results cannot be interpolated to patients on long-acting β -blockers and/or calcium-channel blockers, because these drugs were not studied, not as yet being available for clinical use in the United States at the start of our study. Further studies are warranted in cardiac patients treated with long-acting β -blockers and/or calcium-channel blockers to establish the safety of our anesthetic technique.

That recovery of wakefulness and spontaneous respirations took more than 7.0 hr is of little concern in patients being ventilated artificially, but sustained postoperative analgesia is an advantage. In contrast,

early return of pain is another drawback of fentanyl-supplemented balanced anesthesia (22,25). None of our patients were given naloxone for antagonism of respiratory depression because the study design called for spontaneous recovery of respiration.

In conclusion, when used as the analgesic component of balanced anesthesia, nalbuphine in combination with diazepam and N₂O provides pain relief without adverse hemodynamic and autonomic changes in patients undergoing cardiac surgery. Tracheal intubation, surgical incision, and sternotomy caused no adverse hemodynamic changes or increases in plasma catecholamine levels. Maintenance of anesthesia and recovery were free of the adverse effects associated with other analgesics, including bradycardia, hypotension, hypertension, chest wall rigidity, prolonged respiratory depression, and delayed recovery of spontaneous respiration. This anesthetic technique may be considered an alternative to currently used fentanyl-based anesthetic techniques for cardiac surgical patients.

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Comparison of Midazolam and Thiopental for Rapid Sequence Anesthetic Induction for Elective Cesarean Section

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BLAND BAR, LAWES EG, DUNCAN PW, WARNELL I, DOWNING JW. Comparison of midazolam and thiopental for rapid sequence anesthetic induction for elective cesarean section. *Anesth Analg* 1987;66:1165-8.

Sixty healthy mothers undergoing elective cesarean section received at random either midazolam 0.2 mg/kg or thiopental 3.5 mg/kg with succinylcholine 1 mg/kg for rapid sequence intravenous anesthetic induction. Maintenance of anesthesia was identical in all patients: 50:50 N₂O in oxygen, halothane 0.5% and pancuronium 0.05 mg/kg. Hemodynamic responses were similar, as were the biochemical status of mothers and infants, and maternal to fetal blood gas/acid base gradients. Correlation between maternal arterial and fetal (umbilical venous/arterial) pH, PCO₂ and base excess

values were statistically better with midazolam. However, 1-min Apgar minus color (A - C) scores < 5/8 (representing "severe" neonatal depression) were recorded in five infants after midazolam, three of whom required tracheal intubation, and one whose mother was given thiopental. This difference reached statistical significance (P < 0.05). It is concluded that midazolam is less suitable than thiopental for anesthetic induction in patients undergoing cesarean section.

Key Words: ANESTHESIA—obstetric. ANESTHETICS, INTRAVENOUS—thiopental, midazolam. HYPNOTICS, BENZODIAZEPINES—midazolam. INDUCTION, ANESTHETIC—thiopental, midazolam.

Rapid sequence induction of anesthesia is advocated in all patients likely to regurgitate and aspirate acidic gastric contents (1). Obstetric patients differ from other patients at risk in that they are usually healthy and therefore physiologically normal. Thiopental and succinylcholine have certain disadvantages when used in rapid sequence. Barbiturate-related hypotension may jeopardize the fetus by reducing blood flow to, and exchange across, the placenta. Succinylcholine-induced muscle fasciculations of the anterior abdominal wall can raise maternal intragastric pressure, thus increasing the chance of regurgitation and pulmonary aspiration of gastric contents.

Midazolam, a water soluble benzodiazepine, affects the cardiovascular system minimally, even in patients with already compromised coronary perfusion (2). Another advantage of this new IV induction agent is its anterograde amnesic effect in patients nor-

mally lightly anesthetized before delivery (3), and therefore subject to awareness during surgery.

We therefore investigated on a random basis the use of midazolam and thiopental for rapid sequence induction of anesthesia in healthy patients undergoing elective cesarean section. The mothers were interviewed postoperatively and the neonates assessed by the same observer who was unaware of the induction agent used, to identify adverse maternal sequelae and to assess the effects of the drugs on the early neonatal neurobehavioural scores.

Patients and Methods

Sixty healthy mothers (ASA rating I) undergoing elective cesarean section for cephalopelvic disproportion without other complications of pregnancy were studied with their informed consent. The investigation was approved by the Ethics and Standards Subcommittee of the Board of the Faculty of Medicine, University of Natal, the Medicines Control Council of South Africa and the Natal Provincial Administration.

All parturients were transported to the operating theatre lying on their sides after ingesting 30 ml 0.3

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M sodium citrate, having fasted for at least 8 hours. Patients were placed on the operating table in the left lateral tilt position and baseline blood pressures (automated oscillotonometer) and heart rates (R wave of the ECG) were recorded. A 16-g intravenous cannula was inserted under local anesthesia. Thereafter, 500–750 ml of a balanced salt solution (lactated Ringers) was infused. Domperidone 10 mg followed by glycopyrrolate 0.4 mg were injected IV while patients breathed 100% O₂ through an ADE anesthetic system in the Mapleson A mode (4,5).

Intravenous induction of anesthesia commenced with either midazolam 0.2 mg/kg or thiopental 3.5 mg/kg followed immediately by succinylcholine 1 mg/kg. Cricoid pressure was applied during induction by an experienced assistant until a tracheal tube had been correctly placed and the cuff inflated. The choice of induction agent given rested on the use of a random numbers table.

Ventilation was controlled in all patients with 50:50 N₂O:O₂ (fresh gas flow of 100 ml·kg⁻¹·min⁻¹) and 0.5% halothane via the ADE anesthetic system now in the Mapleson E mode (6,7). The latter allows reasonable clinical control of the patient's PaCO₂ (7). Pancuronium 0.05 mg/kg was given IV to maintain continuous muscle relaxation. A heparinized maternal radial arterial blood sample was drawn immediately before delivery of the infant.

After delivery, the mother received either meperidine 1.5 mg/kg or papaveretum 0.2 mg/kg and an infusion of oxytocin (20 IU in 1000 ml of balanced salt solution) IV. The inhaled nitrous oxide concentration was increased to 70%. Heparinized samples of umbilical venous and arterial blood were taken immediately after birth from a double-clamped section of cord and stored on ice with the maternal arterial sample for subsequent blood gas/acid base analyses (Radiometer ABL 2 automated blood gas analyzer).

Blood pressure (Sentry automated oscillotonometer) and heart rate (R wave of the ECG) were monitored and recorded before anesthesia (baseline), then at 2 min and again, every 5 min after induction. Time from induction to delivery (IDI—to the nearest half minute) and from uterine incision to delivery (UDI—in seconds, timed with a stopwatch) were recorded.

At termination of surgery, residual muscle relaxation was reversed with IV neostigmine (3.75 mg) and glycopyrrolate (0.8 mg). Adequacy of muscle function was judged by the patient's ability to raise her head for > 5 sec, and to maintain an adequate tidal volume as judged by movement of the anesthetic reservoir bag.

The status of the newborn infants was assessed using maternofetal blood gas/acid analyses, modified

Table 1. Maternal and Fetal Blood-Gas and Acid-Base Data Associated with Thiopental and Midazolam Induction of Anesthesia

	Thiopental		Midazolam		P Value
	Mean	SD	Mean	SD	
Maternal artery					
pH	7.34	0.05	7.34	0.03	NS
PCO ₂ (kPa)	5.33	0.76	5.16	0.50	NS
BE (mmol/L)	-4.45	1.68	-4.62	1.89	NS
Umbilical artery					
pH	7.24	0.05	7.25	0.04	NS
PCO ₂ (kPa)	7.56	1.13	7.22	0.72	NS
BE (mmol/L)	-4.95	2.74	-5.32	2.45	NS
Umbilical vein					
pH	7.28	0.05	7.29	0.04	NS
PCO ₂ (kPa)	6.65	1.00	6.35	0.49	NS
BE (mmol/L)	-4.45	1.87	-4.68	2.14	NS

Abbreviation: BE, base excess.

Apgar minus color (A – C) scoring; time to sustained neonatal respiration (TSR); and early neonatal neurobehavioral scoring (ENNS) 4 and 24 hours after delivery. The ENNS assessments were performed by a trained nurse observer unaware of the induction agent used. The mothers were interviewed on the first post-operative day by the same skilled nurse to determine the incidence of intraoperative factual recall (maternal awareness).

Anesthetic maintenance after delivery, patient management, and neonatal aftercare were identical in the two study groups. Statistical analyses of the data comparing the two groups were carried out using the unpaired Student's *t*-test (parametric data) and the χ^2 -test with Yates correction (nonparametric data). Correlation coefficients were calculated using Daisy stats on an Apple IIe computer. *P* < 0.05 was considered statistically significant for this study.

Results

Four patients in each group were excluded because one or more data points were absent, e.g., incomplete neonatal records, clotted blood specimens, copy of anesthetic record missing, and so on. The remaining populations (*n* = 26) in both the thiopental and midazolam groups, respectively, were similar as to mean ($\pm$ SD) age, 25.5 yr ($\pm$ 5.2) and 25.5 ($\pm$ 3.8), and weight 74.3 kg. ($\pm$ 10.3) and 74.1 ($\pm$ 11.2). Mean ($\pm$ SD) IDI in minutes and UDI in seconds (thiopental vs midazolam) were also comparable; 11.2 ($\pm$ 3.9) and 11.5 ($\pm$ 5.7) min; and 104.3 ($\pm$ 122.5) and 72.6 ($\pm$ 60.5), respectively.

The maternal and neonatal blood gas analyses for the thiopental and midazolam groups were comparable (Table 1). Mothers in both groups had evidence

Table 2. Maternal and Fetal Blood-Gas Differences (Ma-Uv; Ma-Ua Gradients)

	Thiopental		Midazolam		P Value
	Mean	SD	Mean	SD	
pH					
Ma-Uv	0.05	0.05	0.05	0.03	NS
Ma-Ua	0.09	0.06	0.09	0.04	NS
P _{CO₂}					
Ma-Uv	1.32	1.04	1.18	0.36	NS
Ma-Ua	2.23	1.14	2.06	0.75	NS
BE					
Ma-Uv	0.03	1.85	0.54	1.49	NS
Ma-Ua	0.49	2.76	0.70	2.22	NS

of mild metabolic acidemia, presumably due both to 12 hours of fasting and the patients' low socio-economic status. Maternal to fetal blood-gas and acid-base differences were similar (Table 2).

Relations between maternal and fetal blood gas/acid base values in the thiopental group were statistically significant only in that maternal arterial pH and base excess (BE) correlated with umbilical vein pH and BE values ($P < 0.02$). In contrast, only a single factor did not correlate significantly in the midazolam series, namely maternal arterial and umbilical vein P_{CO₂} (Table 3).

With regard to relations between time intervals and fetal blood gas/acid base values or maternal-fetal differences in the thiopental group, IDI correlated negatively with umbilical vein (Uv) bicarbonate ($P < 0.05$). In the midazolam group, a negative correlation was found ($P < 0.05$) between IDI and umbilical artery pH and base excess, and positive correlation with (Ma-Ua) pH. There was no statistically significant correlation between UDI values and any other parameter in either group.

Five neonates in the midazolam group were severely depressed (1-min A - C score $< 5/8$), three requiring tracheal intubation and IPPV. Only one infant had a 1-min A - C score $< 5/8$ in the thiopental series; this infant was resuscitated without tracheal intubation. This difference between the study groups was statistically significant at the $P < 0.05$ level (χ^2 -test with Yates correction).

Mean ($\pm$ SD) TSR values (seconds) in the two groups were 54.8 ± 81.1 (midazolam) and $29.8 (\pm 80.5)$ (thiopental); not statistical significance. There were no significant differences in ENNS at 4 and 24 hours between the two groups.

The site of IV injection of the induction agent was inspected at the 24 hour visit and no evidence of significant thrombosis was found in either group. Hemodynamic responses associated with the two induction

Table 3. Correlation Coefficients of Maternal and Fetal Blood-Gas/Acid-Base Values

	Thiopental	P	Midazolam	P
pH				
Ma:Uv	0.458	0.02	0.707	0.001
Ma:Ua	0.300	NS	0.47	0.02
P _{CO₂}				
Ma:Uv	0.326	NS	0.281	NS
Ma:Ua	0.316	NS	0.733	0.001
BE				
Ma:Uv	0.46	0.02	0.733	0.001
Ma:Ua	0.246	NS	0.537	0.01

agents were similar in magnitude. No patient complained of or admitted to awareness during surgery.

Discussion

Midazolam is a relatively short-acting (8), water-soluble benzodiazepine with few hemodynamic effects (2,9) but with significant anterograde amnesic properties (3). A drug offering cardiovascular stability while limiting the chances of intraoperative recall lends itself admirably to use as an induction agent for cesarean section. Elective cesarean section is usually performed in healthy, unpremedicated mothers and traditionally is based on the use of a "light" general anesthetic. The anterograde amnesic effect of midazolam lasts about 20 minutes. The drug might, therefore, be expected to decrease maternal factual recall or awareness during cesarean section, a problem that still remains unresolved in obstetric anesthesia (10). In this study, no patient could recall any part of the procedure after the mask was positioned for preoxygenation, a finding probably attributed to the regular supplementation of anesthesia with halothane 0.5%, rather than to any influence of the induction agents when used in Durban, South Africa at sea level. At higher altitudes, however, the incidence of intraoperative recall during cesarean section may be greater, especially when N₂O in oxygen is used without supplemental IV drugs (11).

There were no significant differences in the hemodynamic changes occurring with induction and after tracheal intubation between the midazolam and thiopental groups. However, IDI correlated better with uterine arterial and (Ma-Ua) pH values in the midazolam group than it did in the thiopental group. The better correlation between maternal and fetal biochemical values seen with midazolam upholds its reputation for promoting cardiovascular stability and may indicate that placental perfusion was better main-

tained with midazolam. Maternofetal blood gas/acid base parameters were, nevertheless, similar in the two groups.

Close perusal of TSR values showed that six infants in the midazolam group required 60 sec or longer to establish a regular breathing pattern, compared with only two infants in the thiopental series. Further statistical analysis (χ^2 -test with Yates correction), after dividing TSR values into 15, 15 to 60, and 60 sec, revealed a statistically significant difference ($P < 0.05$) unfavorable toward midazolam. On the other hand, there was a positive correlation between TSR and IDI in the midazolam group ($P < 0.02$), suggesting that residual aorto-caval occlusion may have been partially responsible for this finding. TSR was unrelated to any other factor in both series.

In a recent study of the placental transfer of midazolam and its metabolite, 1-hydroxymethyl midazolam, in the pregnant ewe (12), the fetal/maternal plasma concentration ratio was 0.15 and the half-lives of both midazolam and its metabolite were identical in mother and fetus. Midazolam, which has a duration of action of 2-3 hours (12,13), adversely affected both infant A - C scores and TSR values in the present study. The early neonatal neurobehavioral scores (ENNS) were not influenced by midazolam, however; probably because ENNS scoring was performed 4 hours after delivery when the sedative effect of midazolam could be expected to have dissipated.

In conclusion, from the maternal viewpoint, midazolam proved an effective intravenous induction agent for elective cesarean section, comparable in most respects to thiopental. Midazolam has some theoretical advantages for the mother, particularly with regard to the hemodynamic stability it produces (2,9,14) and its amnesic action, given that maternal awareness is a potential problem during elective cesarean section (10,11). Midazolam could also benefit the hypertensive patient requiring emergency general anesthesia and cesarean section for moderate to severe pre-eclampsia (12).

However, the condition of the infants immediately after birth was better after thiopental induction in our study. Therefore, midazolam should probably be reserved as an alternative induction agent for those cases in obstetric anesthesia in which a relative or absolute contraindication to the use of a barbiturate exists (e.g., asthma or pregnancy-induced or aggravated hypertension with renal insufficiency). It is interesting to speculate whether midazolam might, by virtue of the

drug's anxiolytic and sedative properties, favor the distressed fetus in utero by reducing maternal catecholamine production, an avenue of investigation perhaps worthy of further pursuit (15,16).

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Dezocine-MAC Reduction and Evidence for Myocardial Depression in the Presence of Enflurane

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Dezocine-MAC reduction and evidence for myocardial depression in the presence of enflurane. *Anesth Analg* 1987;66:1169-74.

The effect of dezocine, an agonist-antagonist opioid analgesic, on enflurane MAC (EMAC) was measured in dogs and, in a separate study, the hemodynamic effects of IV bolus doses of dezocine in the presence of a stable end-tidal enflurane concentration were measured. Study 1 (n = 8)—EMAC Reduction: Dezocine reduced EMAC in a dose-dependent fashion by a maximum of $58 \pm 3\%$ (mean $\pm$ SEM) after injection of 20 mg/kg. Cardiac toxicity prevented administration of higher doses. Study 2—Hemodynamics: Group 1 (n = 7) received dezocine 0.2, 1.5, 5, and 20 mg/kg IV each as a bolus over 30 sec. Group 2 (n = 5)

was studied in exactly the same manner except that instead of dezocine, each dog received drug carrier solution alone (carrier). Significant hemodynamic differences between carrier and drug groups were observed only at the 20 mg/kg dose level, which produced death in one dog and a decrease in mean aortic pressure to $39 \pm 5\%$ of baseline, in cardiac output to $60 \pm 9\%$ of baseline, and in stroke volume to $69 \pm 9\%$ of baseline in the remaining dogs. It is concluded that dezocine produces a dose-dependent reduction in EMAC limited by cardiovascular toxicity. This toxicity appears to be related to direct myocardial depression by high doses of dezocine in the presence of enflurane.

Key Words: ANESTHETICS, VOLATILE—enflurane.
ANALGESICS—dezocine.

Dezocine (WY-16,225) is an agonist-antagonist opioid currently undergoing clinical trials (1-5). In animals its onset and duration of action are similar to morphine but dezocine is up to 17 times more potent than morphine as an analgesic (6-8). Clinical studies to date have been limited to measurements of dezocine analgesia in the postoperative period. Its efficacy as an anesthetic agent has not been determined. One measure of anesthetic efficacy is the ability to reduce the minimum alveolar concentration (MAC) of an inhalation anesthetic (9-12). Intravenous opioids associated with stable hemodynamics may be useful as anesthetic agents either alone or in combination with other central nervous system depressants (13). This study was designed to quantitate the degree of reduction in the MAC of enflurane produced by dezocine and to determine the hemodynamic effects of increasing intravenous doses in the presence of stable end-tidal concentrations of enflurane in the dog.

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Methods

This study was approved by the Emory University Animal Care Committee and followed the guidelines established by that committee for the ethical use of animals for research purposes.

Mongrel dogs ($n = 20$) weighing 17.3 ± 1.1 kg (all results expressed as mean $\pm$ SEM) were given succinylcholine 0.12 ± 0.009 mg/kg (14) and atropine 0.11 ± 0.007 mg/kg. Anesthesia was then immediately induced with 5% enflurane in a high flow of oxygen utilizing a specialized mask and a Bain anesthesia circuit (15), after which a cuffed endotracheal tube was inserted and a Harvard respirator was used to maintain arterial blood gas tensions within the normal range. Enflurane anesthesia was maintained (end-tidal concentration 2.1-2.7%) while monitors were placed. An IV infusion of Ringer's lactate in 5% dextrose was administered at a rate of 15.6 ± 1.3 ml·kg⁻¹·hr⁻¹. Heart rate and rhythm were monitored by electrocardiography, and body temperature was maintained within 1.7°C of the temperature measured at the beginning of the experiment. Arterial blood gas tensions and pressures were monitored via a femoral arterial catheter. End-tidal enflurane was measured utilizing

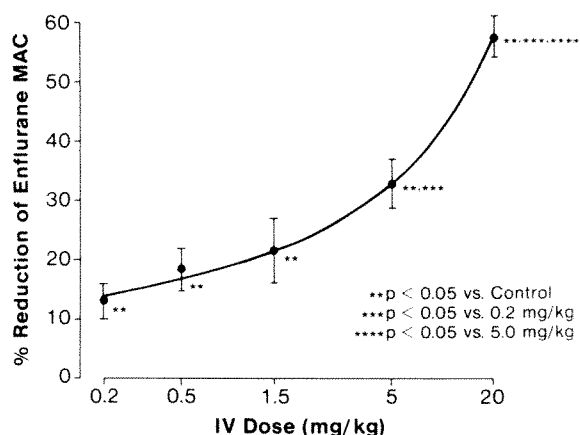


Figure 1. Percent reduction in enflurane MAC produced by incremental doses of dezocine. Each point represents the mean ($\pm$ SEM) reduction in enflurane MAC produced by the indicated single dose (mg/kg) of dezocine administered over 30 sec after a dosage interval of approximately 60 min. (The cumulative dose is not shown).

a Beckman LB-2 infrared analyzer. Two separate studies involving different dogs were undertaken.

Study 1—MAC Reduction

Eight dogs received no additional muscle relaxants. MAC determinations were made according to the technique of Eger et al. (16) and as previously described in other studies from this laboratory (9–11). The use of a Bain anesthesia circuit and high flows of oxygen (6 L/min) permits rapid changes (within 5 min) in end-tidal enflurane concentrations. After the induction of anesthesia, the base of the dog's tail was shaved. After an initial anesthetic equilibration period of 1 hour and in the presence of stable end-tidal enflurane concentrations for at least 15 min, a 25-cm sponge-clamp was applied to the base of the tail and closed to full ratchet lock. The tail was then continuously moved with the clamp until either 1 min elapsed or gross purposeful movement was elicited. Purposeful movement was defined as gross movement of the head or extremities and did not include swallowing or an increased respiratory effort. MAC was determined to the nearest 0.1% end-tidal enflurane, determined in a bracketed fashion by at least three applications of the tail-clamp stimulus (9). After determination of each dog's baseline MAC (i.e., enflurane alone), the first dose of dezocine was administered IV over 30 sec. Because the onset and duration of CNS activity of dezocine are similar to morphine (1,3–5) MAC determinations began after an observation period of 20 min. MAC determinations were completed within 60–90 min at each dose level. After determination of MAC, the next incremental dose of

Table 1. Reduction of Enflurane MAC (Minimum Alveolar Concentration) Produced by Incremental Doses of Dezocine

n ^a	Dose (mg/kg)	Enflurane MAC (mean end-tidal conc.) (% $\pm$ SEM)	Percent reduction of enflurane MAC (% $\pm$ SEM)
8	Baseline	2.17 $\pm$ 0.07	0.0
6	0.2	1.84 $\pm$ 0.09	13.1 $\pm$ 3.1 ^b
6	0.5	1.78 $\pm$ 0.11	18.4 $\pm$ 3.6 ^b
6	1.5	1.65 $\pm$ 0.11	21.4 $\pm$ 5.3 ^b
8	5.0	1.46 $\pm$ 0.08	32.5 $\pm$ 4.2 ^{b,c}
8	20.0	0.89 $\pm$ 0.08	57.5 $\pm$ 3.4 ^{b,c,d}

^aNumber of dogs studied at each dose level.

^bSignificant MAC reduction ($P < 0.001$) from baseline MAC produced by injection of the indicated dose.

^cSignificant MAC reduction ($P < 0.05$) from that produced by 0.2 mg/kg.

^dSignificant MAC reduction ($P < 0.001$) from that produced by 5.0 mg/kg.

dezocine was then administered and the process repeated. Six dogs received dezocine 0.2, 0.5, 1.5, 5, and 20 mg/kg, whereas two dogs received dezocine 5, 20, and 80 mg/kg. Differences between control enflurane MAC and enflurane MAC after the first dose of dezocine were compared using Student's *t*-test. Any further differences in the average enflurane MAC reduction produced by subsequent incremental doses were tested by a one-way analysis of variance.

Study 2—Hemodynamics

While maintaining paralysis with vecuronium 0.1 mg/kg and end-tidal enflurane at 1% for the duration of the experiment, the hemodynamic changes produced by dezocine were recorded. The right external jugular vein was cannulated and a 7F flow-directed thermodilution catheter with a proximal port 15 cm from the tip (American Edwards Laboratories model 93A-095-7F) was introduced. Cardiac output (CO) was measured using an American Edwards Cardiac Output Computer model 9520. Mean aortic pressure (MAP), central venous pressure (CVP), pulmonary artery pressure (PAP) and pulmonary artery occlusion pressure (PAOP) were measured utilizing Cobe disposable strain gauge transducers through an 8-channel Hewlett-Packard System 7758B analyzer. After a 60-min stabilization period during which time baseline measurements were made, the dogs were subdivided into two groups. In the *drug group*, seven dogs received a series of increasing doses of dezocine (0.2, 1.5, 5.0, and 20.0 mg/kg) each administered IV over 30 sec. For each dose, hemodynamic measurements were made before drug injection, at the end of the 30-sec injection (time zero), and at 30, 60, 90, and 120-sec intervals. A 60-min observation period elapsed between each injection and another set of measure-

Table 2. Hemodynamic Variables Measured *Before* Injection of Incremental Doses of Dezocine IV over 30 sec or Equivalent Volume of Carrier Solution (Mean $\pm$ SEM)

Variable	<i>n</i> ^a	Baseline ^b	1.5 ^c	5.0 ^c	20 ^c	15 Min Post ^d
MAP (mm Hg)						
Dezocine	6	131 $\pm$ 5	122 $\pm$ 7	125 $\pm$ 6 ^e	136 $\pm$ 9 ^e	141 $\pm$ 8 ^e
Carrier	5	118 $\pm$ 6	104 $\pm$ 7	104 $\pm$ 8	100 $\pm$ 8	105 $\pm$ 5
CO (L/min)						
Dezocine	4	4.88 $\pm$ 0.35	5.21 $\pm$ 0.50	5.33 $\pm$ 0.69	5.16 $\pm$ 0.86	4.36 $\pm$ 0.65
Carrier	5	4.51 $\pm$ 0.83	4.41 $\pm$ 0.60	5.08 $\pm$ 0.80	5.18 $\pm$ 0.96	5.52 $\pm$ 1.00
SV (ml/beat)						
Dezocine	4	32 $\pm$ 3	35 $\pm$ 5	38 $\pm$ 7	36 $\pm$ 7	34 $\pm$ 6
Carrier	5	29 $\pm$ 4	31 $\pm$ 3	31 $\pm$ 3	35 $\pm$ 5	38 $\pm$ 5
PVR (dynes $\cdot$ sec $\cdot$ cm ⁻⁵)						
Dezocine	4	166 $\pm$ 37	110 $\pm$ 23	131 $\pm$ 17	148 $\pm$ 37	132 $\pm$ 31
Carrier	5	151 $\pm$ 52	146 $\pm$ 38	125 $\pm$ 31	122 $\pm$ 23	120 $\pm$ 22
SVR (dynes $\cdot$ sec $\cdot$ cm ⁻⁵)						
Dezocine	4	2063 $\pm$ 286	1869 $\pm$ 323	1951 $\pm$ 346	2325 $\pm$ 504	2730 $\pm$ 501
Carrier	5	2183 $\pm$ 275	1926 $\pm$ 283	1723 $\pm$ 318	1694 $\pm$ 362	1700 $\pm$ 383

Abbreviations: MAP, mean systemic pressure; CO, cardiac output; SV, stroke volume; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

^a*n*, number of dogs on which the calculations are based. See text for exclusions.

^bBaseline, measurements made in the presence of enflurane alone and before injection of the first dose of dezocine.

^cMeasurement made before injection of the indicated dose of dezocine (mg/kg IV over 30 sec) or equivalent volume of drug carrier solution (carrier). After each injection of drug or carrier except the last injection, a 60 min observation period elapsed.

^d15 min post, observations made 15 min after the final injection of dezocine or carrier.

^e*P* < 0.05 vs carrier.

ments was made before the next injection of dezocine. After injection of the 20 mg/kg dose a 15-min observation period elapsed and the hemodynamic measurements were then repeated. In the *drug carrier solution group*, five dogs were studied in exactly the same fashion except that instead of receiving dezocine, each dog received the equivalent volume of drug carrier solution (containing 5.0 mg monothioglycerol, 0.2 ml propylene glycol, and water for injection to 1 ml).

Differences between the carrier solution and drug groups at any particular dosage and time interval were tested using the BMDP2V-analysis of variance and covariance with repeated measures program by BMDP Statistical Software, Inc. (Los Angeles, CA). The statistical analysis was performed on two groups of data. The first group consisted of the measured hemodynamic variables HR, MAP, PAP, CVP, and PAOP determined before injection (i.e., control), then at the end of the 30-sec injection (time 0) and at 30, 60, 90, and 120 sec after injection. Differences between the means for drug (*n* = 7) and carrier solution (*n* = 5) groups were determined over time for all doses. Data from one dog in the drug group were removed from the entire study because death occurred after injection of the 20 mg/kg dose. Data from another dog were removed from the drug group only for analysis of the differences in the PAOP (catheter malfunction). The second group of data consisted of measurements derived from estimation of the cardiac output (CO) and included stroke volume (SV), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR)

at control, 60, and 90 sec. The results from three dogs in the drug group were removed from the analysis because of death (*n* = 1) or catheter malfunction at one or more data points (*n* = 2). Differences in the means between drug (*n* = 4) and carrier solution (*n* = 5) groups were measured over time from the end of injection. To test the potential cumulative effects of dezocine, the hemodynamic variables measured before each injection of drug were compared to baseline (i.e., enflurane alone) and to the corresponding value after the drug carrier solution alone by *t*-test. *P* < 0.05 was considered statistically significant.

In both studies, provision was made to treat hypotension by administration of additional crystalloid and phenylephrine. Phenylephrine does not interfere with the determination of MAC (17).

Results

Study 1—MAC Reduction

Dezocine produced a dose-related reduction in enflurane MAC (Fig. 1). The lowest dose (0.2 mg/kg) produced a significant mean reduction of enflurane MAC of 13.1 $\pm$ 3.1%. The maximum reduction (57.5 $\pm$ 3.4%) occurred with the 20 mg/kg dose and no ceiling effect was observed (Table 1; Fig. 1).

Data for the 80 mg/kg dose are not included because this dose produced uniformly fatal hypotension that could not be corrected with fluid administration and large doses of phenylephrine (1100 μ g over 2

min). Three of six dogs given 20 mg/kg also required phenylephrine to maintain their blood pressure.

Enflurane MAC remained constant under experimental conditions similar to those used in the present study for at least 8 hr (10).

Study 2—Hemodynamics

In dogs given the drug carrier solution only, there was a decline in mean aortic pressure determined before administration of each dose of carrier solution (118 ± 6 mm Hg with enflurane alone to 100 ± 8 mm Hg before administration of a volume of carrier solution equivalent to a 20 mg/kg dose; Table 2). This was associated with a decrease in systemic vascular resistance (2183 ± 275 to 1694 ± 362 dynes-sec-cm⁻⁵). These changes led to statistically significant differences between the comparable "control" mean aortic pressures measured before each injection of dezocine or carrier solution; the difference between control pressures was first evident before administration of the 5 mg/kg dose or equivalent volume of drug carrier solution (Table 2). The mean aortic pressure in the dezocine group did not differ from baseline (enflurane alone) before injection of any dose of dezocine.

The influence of antecedent doses of dezocine on the hemodynamics measured before any other subsequent dose was minimal (Table 2). There were no significant differences between the values of the hemodynamic variables measured before each dose and baseline values (i.e., enflurane alone). Statistically significant differences between the drug vs carrier solution groups were observed for MAP, CO, and SV at only the 20 mg/kg dose level (Fig. 2; Table 3). After administration of dezocine 20 mg/kg, there was a significant reduction in mean MAP ($39 \pm 5\%$ of the predose [i.e., control] value). This was accompanied by significant declines ($P < 0.05$) in CO to $60 \pm 9\%$ of the predose level and in SV to $69 \pm 9\%$ of control (Table 3). Heart rate declined slightly, accompanied by a rise in PAOP and CVP while SVR, PVR, and PAP remained unchanged. These changes had largely dissipated when the hemodynamic variables were measured 15 min after the 20 mg/kg dose. However, heart rate and cardiac output were still slightly depressed and systemic vascular resistance was elevated (Table 2).

One of the seven dogs given dezocine 20 mg/kg died.

Discussion

Dezocine produced a progressive decrease in enflurane MAC as the dose was increased to 20 mg/kg. The upward slope of the dose-response curve (Fig. 1) sug-

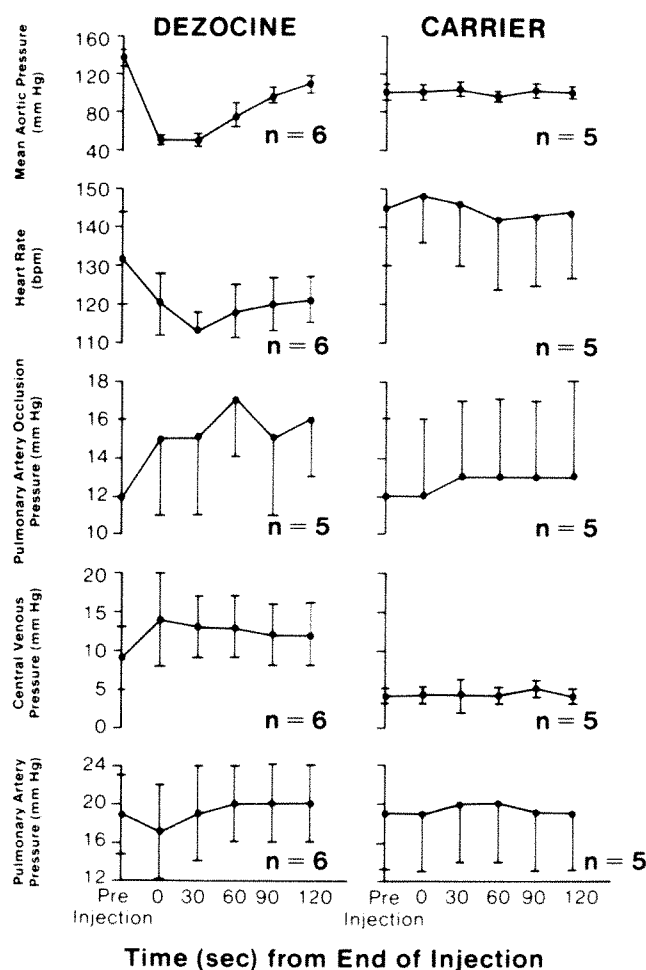


Figure 2. Mean values ($\pm$ SEM) of cardiovascular variables measured from the end of a 30-sec injection (time zero) of dezocine (left panels) or drug carrier solution (right panels). Dezocine 20 mg/kg was injected IV over 30 sec. The drug carrier solution was an equivalent volume of drug diluent containing propylene glycol (0.2 ml/ml solution) administered in exactly the same fashion. Significant differences (by ANOVA) from the control measurement made before injection were observed only for changes in MAP in the dezocine group.

gests that further reductions in MAC might have been produced at higher doses had they not produced cardiovascular toxicity. The 58% reduction of MAC by dezocine (20 mg/kg) was almost equal to the maximum reductions (approximately 65%) produced in the dog under the same experimental conditions by the opioid agonists, morphine and fentanyl (9,10). The decrease in MAC was substantially greater than the maximum MAC reductions achievable with the agonist-antagonist opioids butorphanol and nalbuphine (10). Hence, it appears that dezocine is a more effective anesthetic supplement than other agonist-antagonist opioids, perhaps equivalent to pure agonist opioids in this regard.

However, unlike the pure agonists, doses of dezocine (20 mg/kg or higher) produced transient, severe

Table 3. Hemodynamic Variables Before and After Injection of Dezocine 20 mg/kg or Equivalent Volume of Carrier Solution (Mean $\pm$ SEM)

Variable	Control ^a	60 Sec after injection ^b	90 Sec after injection ^b
MAP (mm Hg)			
Dezocine	136 $\pm$ 9	75 $\pm$ 12 (55 $\pm$ 8) ^c	97 $\pm$ 9 (73 $\pm$ 7)
Carrier	100 $\pm$ 8	97 $\pm$ 6 (98 $\pm$ 3)	102 $\pm$ 8 (102 $\pm$ 2)
CO (L/min)			
Dezocine	5.2 $\pm$ 0.9	3.3 $\pm$ 0.8 (60 $\pm$ 9) ^c	3.6 $\pm$ 0.7 (68 $\pm$ 5)
Carrier	5.2 $\pm$ 1.0	5.5 $\pm$ 1.3 (103 $\pm$ 7)	5.5 $\pm$ 1.0 (106 $\pm$ 8)
SV (ml/beat)			
Dezocine	36 $\pm$ 7	26 $\pm$ 7 (69 $\pm$ 9) ^c	29 $\pm$ 7 (78 $\pm$ 3)
Carrier	35 $\pm$ 5	37 $\pm$ 6 (104 $\pm$ 4)	38 $\pm$ 5 (110 $\pm$ 5)
SVR (dynes $\cdot$ sec $\cdot$ cm ⁻⁵)			
Dezocine	2325 $\pm$ 504	1914 $\pm$ 287 (87 $\pm$ 9)	2184 $\pm$ 313 (100 $\pm$ 10)
Carrier	1693 $\pm$ 362	1748 $\pm$ 514 (98 $\pm$ 7)	1684 $\pm$ 446 (97 $\pm$ 6)
PVR (dynes $\cdot$ sec $\cdot$ cm ⁻⁵)			
Dezocine	148 $\pm$ 37	142 $\pm$ 35 (144 $\pm$ 67)	164 $\pm$ 21 (136 $\pm$ 38)
Carrier	122 $\pm$ 23	122 $\pm$ 28 (100 $\pm$ 8)	95 $\pm$ 21 (81 $\pm$ 10)

Abbreviations as in Table 1.

^aMeasurement made just before injection of drug or carrier solution.^bValues in parentheses represent percent of control value.^c $P < 0.05$ vs control.

hypotension or death in the enflurane-anesthetized dog. At the highest dose, the hypotension was unresponsive to fluid administration and phenylephrine, and appeared to result primarily from myocardial depression as cardiac output and stroke volume decreased in the face of a slight decrease or no change in systemic vascular resistance while cardiac filling pressures remained unchanged or increased slightly. Lewis and Kirchner (8) also observed hypotension in the dog after rapid injection of IV doses of dezocine (2 and 8 mg/kg), but the hemodynamic changes were minimal when these same doses were administered as an infusion over 2 min. Incidentally, they detected no increase in plasma histamine concentrations.

We conclude that dezocine is considerably more effective than other opioid agonist-antagonists as an anesthetic supplement. The use of large doses is, however, limited by cardiac depression. The significance of the hemodynamic effects of large doses of dezocine in patients with cardiovascular disease must be determined by clinical investigation. Clinical studies are warranted because of the potential usefulness of dezocine as an anesthetic supplement. Further an-

imal studies determining the safety of administration of large doses of dezocine by infusion over longer time periods than those employed in this study are also warranted.

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Analgesic Doses of Epidural Morphine Do Not Affect Local Glucose Utilization in the Spinal Cord in Rats

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KURODA Y, NAKAKIMURA K, SAKABE T, MAEKAWA T, TAKESHITA H. Analgesic doses of epidural morphine do not affect local glucose utilization in the spinal cord in rats. *Anesth Analg* 1987;66:1175-9.

The possibility of association between changes in spinal cord metabolism and changes in spinal cord neuronal activity by injection of morphine into the epidural space in amounts adequate to produce analgesia was examined. Fourteen Wistar rats were equally divided into two groups: a morphine group (epidural, 15 μ g) and a control group (saline). Using the 2-[^{14} C] deoxyglucose method, glucose utilization was measured in the spinal cord and in the brain, including

structures related to pain modulation, in the presence and in the absence of analgesia produced by epidural morphine as confirmed by the hot plate test. Glucose utilization was shown to be similar in the spinal cord and in the brain in both groups of animals. The results suggest that analgesic doses of epidural morphine do not affect neuronal activity of the spinal cord by changing spinal cord carbohydrate metabolism.

Key Words: ANALGESICS—morphine. SPINAL CORD—metabolism. ANESTHETIC TECHNIQUES, EPIDURAL—morphine.

Previous studies have shown that pharmacologic and physiologic interventions in the spinal cord are accompanied by metabolic changes reflecting changes in neuronal function (1,2). Despite the wide use of epidural morphine in the management of postoperative or intractable pain, there are no data on the effect of epidural opiates on spinal cord metabolism, except an abstract by Lin et al. (3). They found in rats anesthetized with halothane that analgesic doses of epidural fentanyl attenuated the increase in local spinal cord glucose utilization (LSGU) evoked by somatosensory stimulation. Lack of information on the effect of epidural morphine on spinal cord metabolism in conscious animals prompted us to conduct the present study, in which we measured LSGU as a reflection of functional change. We found that analgesia produced by epidural morphine does not affect LSGU.

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Materials and Methods

The experiments were performed using 19 adult male Wistar rats, weighing 250–300 g, that were allowed free access to food and water until the time of the experiment.

The lumbar epidural space was catheterized during 2% halothane anesthesia as described by Bahar et al. (4). Briefly, a 17-cm length of polyethylene catheter (PE 10) was inserted through a small hole made in the midpoint of the lamina of the L-5 vertebra and advanced 2 cm cephalad, so its tip was located at the L-2 or L-3 level. After the catheter was exteriorized through a second skin incision in the midline over the upper cervical area by tunneling it under the skin, the incisions were closed and the anesthesia was discontinued. The rats were returned to their cages, and neurologic functions assessed for the next 24 hr. None of the rats developed paralysis, spasticity of the hindpaws, and/or an abnormal gait during a 24-hr observation period.

In five rats given 15 μ g morphine hydrochloride dissolved in 40 μ l saline epidurally, the duration of analgesia was evaluated by the tail flick (beam intensity, 60 W; cutoff time, 20 sec) and hot plate (plate temperature, 53°C; cutoff time, 30 sec) tests as described by Durant et al. (5). Response latencies were

expressed as the percentage of the maximal possible effect (MPE):

$$\% \text{MPE} = \frac{\text{postdrug latency} - \text{predrug latency}}{\text{cutoff time} - \text{predrug latency}} \times 100\%.$$

The remaining 14 rats were randomly divided into two equal groups: a morphine group (epidural morphine) and a control group (epidural saline). After 24 hr observation following epidural catheterization, the rats were anesthetized again with 2% halothane for bilateral catheterization of the femoral arteries and veins and partially immobilized with a pelvic plaster cast. Halothane was discontinued, and 3 hr was allowed to elapse before the start of epidural injection. In the control group, 40 μl saline was injected through the epidural catheter. In the morphine group, 15 μg morphine hydrochloride dissolved in 40 μl saline was injected. The analgesic effect was confirmed 10 min after the injection with the hot plate test.

Measurements of local glucose utilization began 15 min after injection of morphine or saline starting with the IV bolus injection of 2-[^{14}C]deoxyglucose (New England Nuclear, specific activity, 51–52 mCi/mmol), 150 $\mu\text{Ci/kg}$ in 0.5 ml saline. Fifteen arterial blood samples were obtained over 45 min with frequent sampling during the early period so as not to miss the peak of the arterial concentration curves. The samples were centrifuged, and the plasma was separated and frozen at -40°C for later determination of 2-[^{14}C]deoxyglucose (2-[^{14}C]DG) and glucose concentrations. Mean arterial blood pressure (MAP) was monitored continuously. Arterial blood gas tensions, pH, and hematocrit were measured and maintained within physiologic limits. Rectal temperature was kept at $37 \pm 0^\circ\text{C}$. Immediately after the final arterial blood sample was obtained at 45 min, the rat was killed by an IV injection of an overdose of pentobarbital and decapitated. The brain and spinal cord were removed quickly and frozen in isopentane cooled to -50°C with Freon. After serial sectioning (20 μm in thickness), the spinal cord and brain tissue sections were exposed to x-ray film (Kodak SB-5) for 10 days, along with a set of calibrated [^{14}C]methylmethacrylate standards (The Radiochemical Center, Amersham, England). Local tissue ^{14}C concentrations were determined from the calibrated ^{14}C standards and optical density measurements made with the use of a computerized image-processing system (UHG-100S1, Unique Medical, Japan). Plasma glucose concentrations were determined with the oxidase method using the Beckman Glucose Analyzer 2. The plasma 2-[^{14}C]DG concentrations were determined in a liquid scintillation counter (Tricarb 4640, Packard).

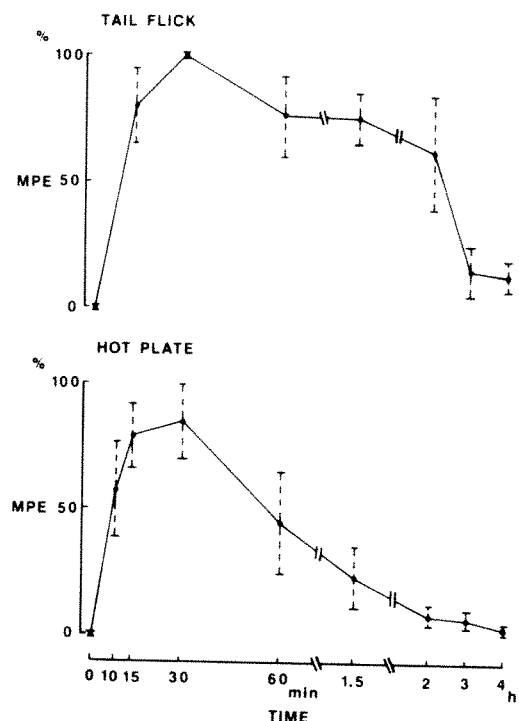


Figure 1. Time course of %MPE on the tail flick and hot plate tests after epidurally administered 15 μg morphine hydrochloride dissolved in 40 μl saline. Each point represents the mean $\pm$ SE of five rats.

Measurements of glucose utilization in the lumbar, thoracic, and cervical spinal cord were made in nine gray and three white matter regions. In the thoracic spinal cord, measurements were made in eight gray regions because this area lacks Rexed lamina VI. Sections immediately adjacent to those used for autoradiography were stained with hematoxylin-eosin for histologic identification of spinal cord structures and for comparing autoradiograms with an atlas of the rat spinal cord (6). Local cerebral glucose utilization (LCGU) in 21 regions including the structures related to pain modulation were also determined. LSGU and LCGU were calculated from the tissue ^{14}C , plasma glucose, and 2-[^{14}C]DG concentrations, and the rate and lumped constants using the equation as described by Sokoloff et al. (7). In their equation, glucose utilization is derived from a kinetic model for the rate of DG and glucose phosphorylation. When given in trace amounts, DG competes with glucose for uptake from plasma and for phosphorylation by hexokinase, but DG is trapped as DG-6-phosphate in the brain after phosphorylation because it does not serve as a substrate for any further metabolic step. Because a Michaelis-Menten relation exists in the rate of metabolism for these competitive substrates, glucose utilization is calculated from the rate of phosphorylation

Table 1. Physiologic Variables*

	Control (n = 7)	Morphine (n = 7)
MAP (mm Hg)	97 ± 3	94 ± 2
PaO ₂ (mm Hg)	90 ± 2	95 ± 2
PaCO ₂ (mm Hg)	41 ± 2	41 ± 2
Arterial pH	7.41 ± 0.02	7.44 ± 0.02
Hematocrit (%)	40 ± 1	39 ± 1

*All values are expressed as mean ± SE.

of DG by hexokinase. The rate of phosphorylation of DG is derived from the accumulation of DG-6-phosphate, which is calculated by mathematical subtraction of unmetabolized DG from the total DG in the tissue.

In an additional three rats, the effect of 15 µg IV morphine was evaluated; no analgesic effect was observed.

The statistical significance of the differences between the two groups was analyzed with an unpaired *t*-test. *P* < 0.05 was considered statistically significant.

Results

The results of the tail flick and hot plate tests expressed as %MPE in five rats given 15 µg morphine epidurally are shown in Figure 1. The duration of analgesia appeared to be adequate to cover the period for the measurement of glucose utilization. In rats that served for the measurement of glucose utilization, analgesia was confirmed 10 min after the injection of epidural morphine with the hot plate test and the %MPE was 56 ± 15 (mean ± SE).

The physiologic variables are shown in Table 1. There were no significant differences between the two groups. PaO₂, PaCO₂, and pH were within normal physiologic limits.

LSGU and LCGU values are shown in Tables 2 and 3. There were no significant differences in LSGU and LCGU between the morphine and the control groups at any of the sites analyzed. LSGU values in gray matter were approximately half those in the somatosensory cortex. Laminae I-II and X showed the lowest and the highest LSGU values in the lumbar gray matter, respectively, this tendency being seen also in the cervical as well as thoracic spinal cord. LSGU values in white matter were less than those in the gray.

Discussion

The results indicate that an analgesic dose of morphine given epidurally has no effect on LSGU and LCGU in conscious rats, even in Rexed laminae I-II of the spinal cord where opiate receptors are densely

Table 2. Local Spinal Cord Glucose Utilization Associated with the Lumbar Injection of Epidural Morphine*

Structures	Control (n = 7)	Morphine (n = 7)
Cervical spinal cord		
Gray matter		
I-II	31 ± 2	30 ± 3
III	36 ± 2	35 ± 3
IV	41 ± 2	40 ± 3
V	43 ± 3	43 ± 3
VI	43 ± 2	43 ± 3
VII	42 ± 2	42 ± 3
VIII	39 ± 2	39 ± 3
IX	37 ± 2	36 ± 3
X	42 ± 2	43 ± 3
White matter		
Dorsal	19 ± 1	17 ± 2
Lateral	21 ± 1	19 ± 2
Ventral	22 ± 1	20 ± 2
Thoracic spinal cord		
Gray matter		
I-II	32 ± 1	31 ± 2
III	36 ± 2	35 ± 2
IV	36 ± 2	36 ± 2
V	38 ± 2	38 ± 2
VII	37 ± 2	36 ± 2
VIII	37 ± 2	35 ± 2
IX	33 ± 2	31 ± 2
X	40 ± 2	39 ± 2
White matter		
Dorsal	18 ± 1	17 ± 1
Lateral	17 ± 0	16 ± 1
Ventral	20 ± 1	17 ± 1
Lumbar spinal cord		
Gray matter		
I-II	34 ± 2	32 ± 2
III	38 ± 2	36 ± 2
IV	41 ± 2	42 ± 2
V	43 ± 3	44 ± 3
VI	45 ± 3	44 ± 2
VII	44 ± 3	43 ± 2
VIII	45 ± 3	42 ± 3
IX	41 ± 3	39 ± 2
X	49 ± 3	47 ± 3
White matter		
Dorsal	20 ± 1	19 ± 1
Lateral	23 ± 1	20 ± 1
Ventral	25 ± 1	21 ± 1

*All values are expressed as mean ± SE (µmol/100 g⁻¹·min⁻¹).

distributed (8). This is in contrast to the report that an anesthetic dose of pentobarbital significantly decreases LSGU and LCGU and that nitrous oxide in analgesic concentration significantly increases LSGU and LCGU (1). The LSGU values in the lumbar spinal cord in the control group in the present study are similar to those reported by Crosby et al. (1). The analgesic effect of epidural morphine on the hind-paws were confirmed with the hot plate test in the present study (see Results). With the same dose of

Table 3. Local Cerebral Glucose Utilization Associated with the Lumbar Injection of Epidural Morphine*

Structures	Control (n = 7)	Morphine (n = 7)
Somatosensory cortex	90 ± 5	85 ± 3
Mediodorsal nucleus of the thalamus	95 ± 5	86 ± 3
Ventrolateral nucleus of the thalamus	90 ± 6	82 ± 3
Medial habenula	66 ± 5	66 ± 3
Limbic system		
Hypothalamus	56 ± 2	53 ± 1
Amygdala	75 ± 5	72 ± 3
Nucleus accumbens	75 ± 4	75 ± 3
Mammillary complex	83 ± 2	82 ± 2
Substantia nigra	67 ± 4	65 ± 3
Interpeduncular nucleus	80 ± 3	80 ± 2
Midbrain reticular formation	63 ± 4	58 ± 2
Pontine nuclei	54 ± 4	58 ± 2
Periaqueductal gray	62 ± 3	55 ± 2
Dorsal raphe nucleus	65 ± 3	59 ± 2
Median raphe nucleus	72 ± 3	63 ± 4
Gigantocellular reticular nucleus	51 ± 2	51 ± 2
Paragigantocellular reticular nucleus	49 ± 3	50 ± 2
Nucleus raphe magnus	44 ± 3	45 ± 2
Trigeminal nerve nucleus	60 ± 2	60 ± 3
Dorsal column nuclei		
Cuneate nucleus	75 ± 7	70 ± 4
Gracile nucleus	56 ± 2	55 ± 1

*All values are expressed as mean ± SE ($\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$).

morphine given intravenously, analgesia was not obtained. Therefore, analgesia by epidural morphine was assumed to be mainly the result of its effect on the spinal cord, as suggested by others (9,10).

Lin et al. (3) reported that epidural fentanyl depressed the evoked metabolic response to somatosensory stimulation in rats anesthetized lightly with halothane, whereas resting LSGU in the absence of afferent stimuli appeared to be minimally affected. However, evaluation of the effect on resting LSGU was made by measuring LSGU in the structures contralateral to stimulation, thus making it difficult to determine the changes in resting metabolic state induced by epidural fentanyl.

We considered the possibility that the absence of a significant difference in LSGU and LCGU in the two groups in the present study may have been because of the small number of animals examined. However, we performed a statistical analysis of power ($1 - \beta = 0.9$) on our data, and the calculations revealed that more than 140 additional rats in each group would be necessary to establish a difference, if it really existed in gray matter, which includes the laminae where opiate receptors are densely distributed. We think it

is statistically unlikely that the present negative results would be changed by increasing the number of animals studied.

The absence of significant changes in LSGU in the morphine group in the present study is best discussed in relation to neuronal activity. If one accepts that local glucose utilization is a reflection of neuronal activity (11), the lack of change in LSGU should reflect unchanged neuronal discharge. Spontaneous activity of the wide dynamic range neurons in the lumbar dorsal horn has been reported to be unchanged with spinally administered morphine in decerebrate, spinal cord-transected (T12) cats (12). In the present study, LSGU levels in the laminae, including Rexed V where the wide dynamic range neurons are, were not statistically different from the control values. This suggests that epidurally or spinally administered morphine does not significantly affect either spontaneous metabolic or neurophysiologic activity in the spinal cord and that there is a close coupling of metabolic activity of these neurons with their discharge frequency, as seen in the cerebral cortex (13).

Our present results obtained in the spinal cord are in accordance with the recent report by Levy et al. (14), who found no change in LCGU with analgesic doses of morphine administered intravenously in rats lightly anesthetized with methohexital. Their results seem to have resolved the differences among previous reports (15,16) that described variable changes in LCGU in both direction and magnitude depending on the structures examined and the doses of morphine used. Thus, it appears that the binding of morphine with opiate receptors in amounts adequate to produce analgesia has no significant effect on metabolism of the central nervous system in conscious and unstimulated rats, indicating that analgesic doses of morphine do not affect the spontaneous neuronal activity even though it is sufficient to inhibit neuronal transmission of noxious stimuli. However, we cannot entirely exclude the possibility that neurons in the central nervous system have been affected by the binding of morphine with opiate receptors, but their metabolic changes were spatially as well as quantitatively unsegregated with the method used in the present study.

In summary, analgesic epidural morphine does not affect spontaneous metabolic activity in the spinal cord in conscious rats.

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Clinical Reports

Comparison of Pain Associated with Intradermal and Subcutaneous Infiltration with Various Local Anesthetic Solutions

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Although used to obtund pain, local anesthetics may themselves initially produce pain on injection (1,2). From a clinical perspective, knowing the degree of pain produced by various agents would be important in selecting a local anesthetic for many surgical procedures. The present study compares the levels of pain associated with intradermal and subcutaneous injections of normal saline and five different local anesthetic solutions.

Methods

The investigation was approved by our hospital's Committee for the Protection of Human Subjects from Research Risks. Twenty-four healthy, young volunteers from the medical and paramedical staff gave informed consent to participate in this study. Five local anesthetics (etidocaine 1%, bupivacaine 0.5%, mepivacaine 1%, chloroprocaine 2%, and lidocaine 1%) and normal saline were tested in each subject; details of each preparation are shown in Table 1. The pKa values, degrees of protein binding, and lipid solubilities have been previously determined (3,4). The pH values were measured on a Corning 140 pH meter. Data concerning additives and sodium chloride concentrations were provided by the manufacturers. Osmolality measurements were made using an Advanced Micro Osmometer 3MO (Advanced Instruments Co.).

Six discrete areas on the volar surface of the left forearm served as areas for injection of the test preparations. A random numbers table was used to assign

preparations to each of the areas. Before injection, the skin was cleaned with 70% isopropyl alcohol and allowed to dry. For each test, 0.1 ml was injected intradermally, then 0.2 ml subcutaneously, the same 26-gauge hypodermic needle on a 1-ml tuberculin syringe being used for the single injection. All injections were performed by the same investigator in a standardized fashion to limit variability of technique. Neither subject nor experimenter was aware of syringe contents. The six injections were made at 15-sec intervals over approximately 2 min. Immediately after each injection, subjects were asked to score the pain of injection using a 10-cm linear analogue pain scale (5-7). Subjects were instructed to score a pain-free injection as zero and the most pain imaginable as 10. Markings on the analogue pain scale were measured to the nearest millimeter and mean pain scores were computed for each treatment group. Agents were ranked from most to least painful, based on the frequency with which subjects assigned highest and lowest pain scores for the particular agent.

The Kruskal-Wallis analysis of variance was used to examine the distribution of pain scores among all agents, and the Wilcoxon Signed Rank test was employed to contrast pairs of agents. Mean pain scores are reported with the standard error of the mean (SEM). A probability value of <0.05 was considered statistically significant.

Results

Etidocaine had the highest mean pain score (64 ± 6) (Fig. 1). Bupivacaine had the next highest score (45 ± 6), followed by mepivacaine (41 ± 5), saline (40 ± 5), chloroprocaine (39 ± 6), and lidocaine (32 ± 5). Analysis of variance indicated a significant non-random distribution. The results of the Wilcoxon Signed Rank tests for the paired comparisons are presented

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Table 1. Physical Characteristics of the Preparations Tested

Agent	pH	Osmolality (mosm/kg)	pKa	Protein-binding	Lipid solubility	Sodium chloride (mg/cc)	Other additives	Manufacturer
Etidocaine 1%	4.7	284	7.7	94	141	7.1	None	Astra
Bupivacaine 0.5%	5.5	281	8.1	95	28	8.0	None	Astra
Mepivacaine 1%	5.6	284	7.6	77	0.8	6.6	Methylparaben	Winthrop-Breon
Saline 0.9%	6.8	308	—	—	—	9.0	None	Abbott
Chloroprocaine 2%	3.4	277	8.7	?	0.14	4.0	Sodium bisulfite	Astra
Lidocaine 1%	6.5	291	7.7	64	2.9	7.0	None	Astra

Table 2. *P*-Values of Paired Comparisons Between Agents

	Lidocaine	Chloroprocaine	Saline	Mepivacaine	Bupivacaine
Etidocaine	0.00001	0.00003	0.00005	0.00005	0.00005
Bupivacaine	0.005	0.03	0.1	0.1	—
Mepivacaine	0.012	0.5	0.3	—	—
Saline	0.046	0.4	—	—	—
Chloroprocaine	0.1	—	—	—	—

in Table 2. Etidocaine was significantly more painful than all other agents and bupivacaine was significantly more painful than lidocaine or chloroprocaine. Both mepivacaine and saline were significantly more painful than lidocaine.

The frequency of agents being rated as most and least painful is shown in Figure 1. Twenty subjects considered etidocaine the most painful agent. No subject considered bupivacaine most or least painful. Mepivacaine was considered most painful by two subjects and least painful by two others. Seven subjects rated chloroprocaine least painful and 2 most painful; no subject considered lidocaine most painful while 11 considered it least painful. As illustrated in Figure 1, the rank order of mean pain scores from highest to lowest is in agreement with the combined frequency distributions of subjects who rated agents most and least painful.

Discussion

The data presented show a marked variation in the pain response to injection of local anesthetics. Etidocaine was clearly the most painful, whereas chloroprocaine and lidocaine were the least painful of the local anesthetics. Bupivacaine and mepivacaine produced intermediate degrees of pain.

The mechanism of pain produced by local anesthetics is unknown. The differences noted do not ap-

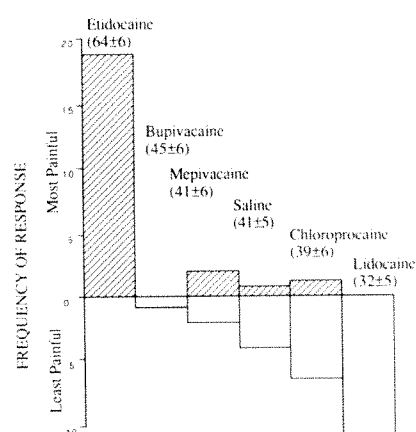


Figure 1. Frequency of subjects considering agent most painful (hatched bars) or least painful (clear bars). Numbers in parentheses at top of bars are mean pain scores $\pm$ SEM.

pear to be related to the formulation of the anesthetic solutions. For example, chloroprocaine, with the lowest pH (3.4), was among the least painful, whereas etidocaine, which has the next lowest pH (4.7), was clearly the most painful local anesthetic. Although increasing the pH of lidocaine by adding sodium bicarbonate decreases the pain on injection (8), this does not appear to be the dominant factor when comparing different agents. In addition, differences in pain perception could not be explained by the sodium chloride concentration in the solutions, osmolality, or by the presence of other additives (Table 1).

With regard to the physical-chemical properties of the agents, no relation existed between ionization (i.e., pKa) or protein-binding and pain production. For example, etidocaine, which was most painful, has a pKa equal to that of lidocaine, the least painful agent. Etidocaine and bupivacaine are similar with respect to protein-binding properties but differed significantly in pain production.

Lipid solubility is the physical characteristic that most closely paralleled the painful effects of the local anesthetics. Etidocaine, clearly the most painful, was the most lipid-soluble. The second most lipid-soluble agent, bupivacaine, was also the next most painful. Chloroprocaine, least lipid-soluble, was among the least painful. However, the relation was not precise; although lidocaine is least painful, it is more lipid-soluble than chloroprocaine or mepivacaine.

In summary, pain caused by intradermal or subcutaneous injection of different local anesthetics varies considerably. Etidocaine was the most painful agent, whereas chloroprocaine and lidocaine were least painful. Bupivacaine and mepivacaine produced intermediate degrees of pain. The mechanism of local

anesthetic-induced pain remains unclear but may be related in part to lipid solubility.

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Electrocardiographic ST-Segment Elevation after Myocardial Reperfusion during Coronary Artery Surgery

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Electrocardiographic (ECG) ST-segment elevation is generally regarded as indicating transmural myocardial ischemia (1,2). Such ECG changes may be observed after myocardial reperfusion during open-heart surgery. For example, during open-ventricle procedures, ST elevation, especially in the inferior ECG leads II, III, and aVF, often indicates air or particulate embolization of the coronary circulation (3). Similar changes have been reported to occur infrequently after coronary artery bypass grafting, as a manifestation of coronary artery spasm (4,5). In addition, we often have noted transient ST elevation during the period of myocardial reperfusion that follows coronary artery bypass grafting. We were uncertain as to the significance of these changes. The following study was undertaken to document the frequency and duration of episodic ST elevation occurring subsequent to myocardial reperfusion at the time of coronary artery bypass grafting and to determine if this phenomenon was associated with morbidity.

Methods

The study was approved by the Committee for Human Experimentation of the University of Manitoba. The committee advised us that the informed consent of the participants would not be required. During a 3-month period, 30 patients undergoing elective coronary artery bypass procedures were studied. Patients with ST-segment elevation, or infranodal conduction

abnormality, in their resting 12-lead ECG were excluded.

On arrival in the operating theatre ECG leads II and CS₅ were applied and continuously recorded for the succeeding 24 hr by a Holter Monitor (Del-Mar Avionics model 445 A or B). Anesthetic management was at the discretion of the attending anesthesiologist. All patients received high-dose fentanyl as the primary anesthetic agent. The distal coronary artery-vein graft anastomoses were performed during hypothermic (25–28°C) cardiopulmonary bypass, while the heart was arrested with cold potassium cardioplegia solution administered every 15–20 min in quantities sufficient to maintain an isoelectric ECG. Myocardial temperature was not monitored. The proximal aorta-vein graft anastomoses were completed using a side-biting aortic clamp during systemic rewarming and myocardial reperfusion.

One of us remained with each patient during anesthesia and surgery, and we recorded and marked on the 24-hr ECG the time of the following intraoperative events: 1) initiation of cardiopulmonary bypass, 2) aortic cross-clamping, 3) removal of the aortic cross-clamp, 4) application of the side-biting aortic clamp, 5) removal of the side-biting clamp, 6) termination of cardiopulmonary bypass, and 7) arrival in intensive care unit. Investigators did not discuss clinical events or ECG changes with either attending anesthesiologists or surgeons. Beginning on the first postoperative day, all patients had serial 12-lead ECG and creatine kinase MB (CK-MB) isoenzyme determinations performed daily for 3 days. These tests are performed routinely on all postoperative cardiac surgery patients at our institution. The 24-hr Holter monitor ECG recordings were reviewed using an Avionics Electrocardioscanner. Elevation of the ST segment of 0.10 mV or more and persisting for 1 min was considered significant. A cardiologist who was unaware of the results of the Holter recordings reviewed the serial 12-lead ECG tracings for new Q waves indicative of

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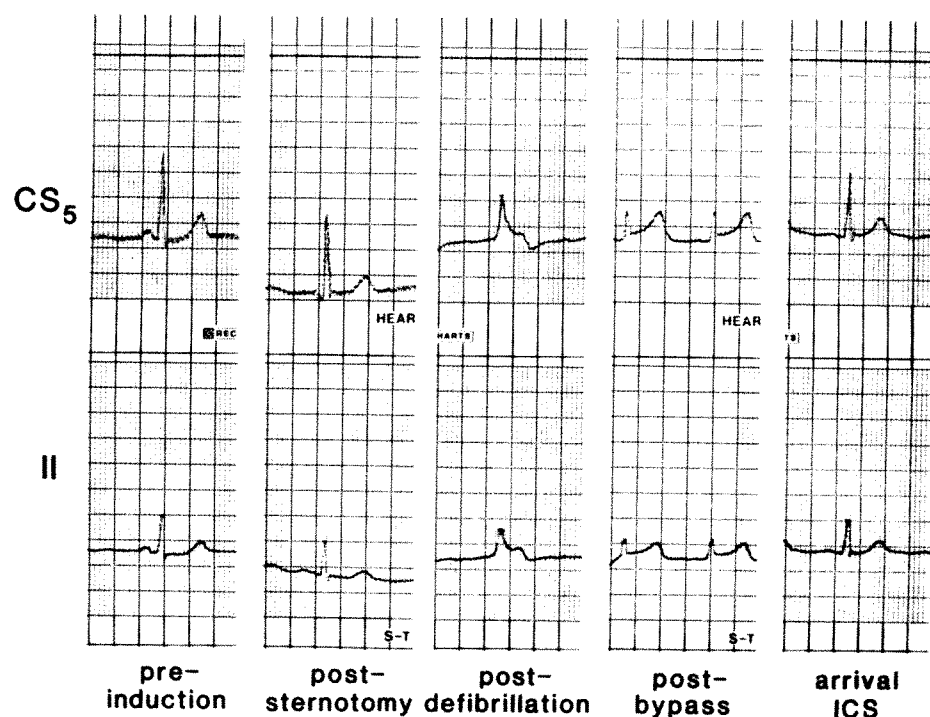


Figure 1. Electrocardiographic tracings from a 69-year-old woman who underwent triple coronary artery bypass grafting. After defibrillation, she developed new ST elevation in both leads II and CS₅ that persisted after bypass but resolved before arrival in the intensive care unit (ICS).

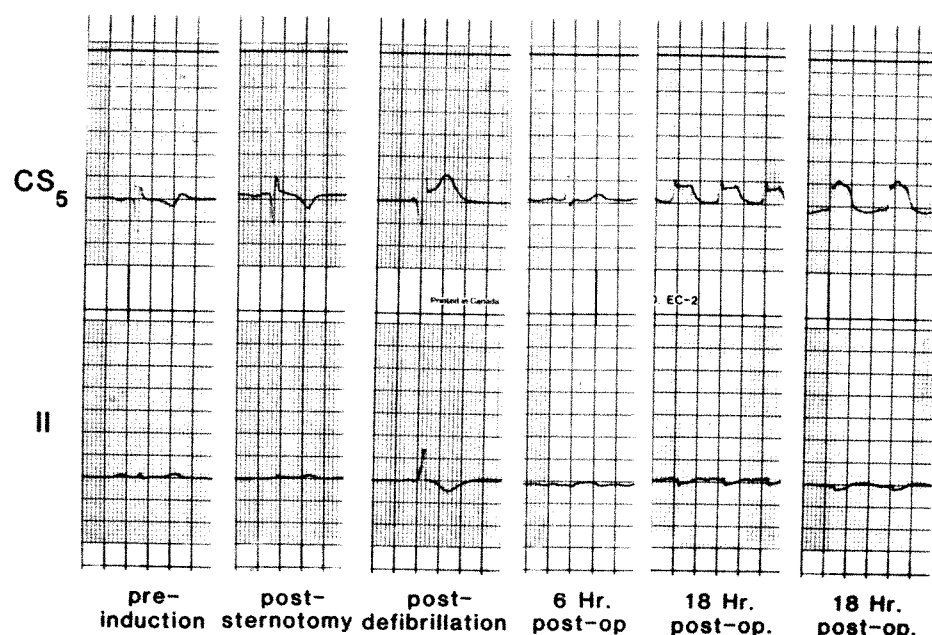


Figure 2. Electrocardiographic tracings from a 65-year-old man who underwent quadruple coronary artery bypass grafting. After defibrillation, he developed transient ST elevation in lead CS₅ that resolved before discontinuance of bypass. Eighteen hours post-operatively he had another episode of ST elevation.

perioperative transmural myocardial infarction. The patients were retrospectively divided into two groups based on the presence or absence of ST segment elevation in their Holter ECG recordings. The demographic characteristics of these two groups were compared using Student's *t*-test, the Wilcoxon Mann-Whitney rank sums test, or Fischer's exact test, where appropriate. The CK-MB isoenzyme fractions from

the two groups were compared by analysis of variance (ANOVA) for repeated measures. Null hypotheses were rejected when *P* values ≤ 0.05 were obtained.

Results

Review of the Holter ECG recordings revealed that none of the patients exhibited significant ST elevation

Table 1. Demographic and Perioperative Variables in Patients with and without ST Elevation^a

Variable	ST elevation (n = 13)	No ST elevation (n = 17)
Age (yr)	57 ± 12	63 ± 9
Male:female	3:10	3:14
Ejection fraction	0.59 ± 15	0.57 ± 16
Angina at rest (n)	5	2
Antianginal medication (n)		
Nitrates	11	15
β-Adrenergic antagonist	12	13
Calcium-entry blocking agent	8	8
Coronary grafts (n)	3.1 ± 1.0	3.3 ± 0.6
Duration of cardiopulmonary bypass (min)	132 ± 43	131 ± 30
Duration of aortic clamping (min)	54 ± 20	54 ± 13
Postbypass therapy (n)		
Inotrope	8	7
Balloon counterpulsation	1	0
New Q waves postoperatively (n)	2	0

^aValues are the incidences or means ± SD.

before cardiopulmonary bypass. Thirteen patients had significant ST elevation at some time subsequent to removal of the aortic cross-clamp. A total of 18 discrete episodes of ST elevation lasting an average of 29 ± 25 min (mean ± SD) were recorded. Eight episodes were apparent in lead II only, four in lead CS₅ only, and six in both leads II and CS₅. Twelve episodes were apparent as soon as a normal supraventricular rhythm resumed after unclamping of the aorta. Three other episodes commenced after cardiopulmonary bypass was discontinued, and three more episodes occurred in the intensive care unit. Representative ECG tracings from two patients are shown in Figures 1 and 2.

Demographic and intraoperative characteristics of patients with and without ECG ST elevation are compared in Table 1. The two groups of patients did not differ with respect to age, sex, preoperative ejection fraction, severity of angina, type of antianginal medications, duration of cardiopulmonary bypass, duration of aortic cross-clamping, number of distal coronary anastomoses performed, or need for postoperative pharmacologic or mechanical circulatory support.

Table 2 summarizes the postoperative CK-MB measurements in the two groups of patients. The CK-MB levels were significantly higher postoperatively in patients with ST-segment elevation in their Holter record. Two patients with ST elevation developed new Q waves indicative of myocardial infarction, whereas there were no new Q waves in patients who did not have ST elevation. The incidence of new Q waves did

Table 2. Postoperative Creatine Kinase MB (CK-MB) Isoenzyme Levels^a

Group	Postoperative Day		
	1	2	3
ST elevation (n = 13)	157 ± 236	71 ± 82	37 ± 33
No ST elevation (n = 17)	68 ± 39	38 ± 21	23 ± 12

^aThe values are the means ± SD. The groups differ significantly with respect to CK-MB levels. $P < 0.05$ by ANOVA.

not differ significantly between groups (Fisher's exact test). The location of new Q waves did not always correspond to the location of transient ST elevation. There were no deaths.

Discussion

The 43% incidence of ST elevation in this study confirms our impression that this is a common event after coronary artery bypass grafting procedures. ST elevation was almost always apparent as soon as a supraventricular rhythm was resumed after reperfusion. In 78% of the episodes the ST elevation was detectable in lead II. Thirty-eight percent of the patients had more than one episode (not always in the same ECG lead), with recurrence either in the postbypass period or while in the intensive care unit. Retrospective analysis of CK-MB isoenzyme concentrations indicated more myocardial damage in patients who exhibited ST-segment elevation.

ST-segment elevation may be a manifestation of transmural ischemia caused by coronary artery embolism, spasm, or thrombosis. Alternatively, epicardial injury, transmural myocardial temperature gradients, or inhomogeneous reperfusion might be implicated. Our study was not designed to determine the etiology of the observed ST changes. However, the results may provide some clues regarding etiology. Clearly, ST-segment elevation is not an inevitable consequence of reperfusion after a period of cardioplegic arrest, because many patients in this study had isoelectric ST segments starting with the first beat after resumption of a supraventricular rhythm. The finding of increased CK-MB levels postoperatively in patients with ST elevation supports an ischemic etiology. The frequency of ST elevation in lead II suggests the right ventricle as the region most commonly affected. Both air embolism and coronary artery spasm have a predilection for involving the right coronary artery (3-5). However, systemic air embolism is presumed to occur less frequently after coronary artery bypass procedures, compared with open-ventricle

procedures (6). We expected coronary air embolism to occur at the time of removal of the side-biting aortic clamp after completion of the proximal aortic anastomoses. However, in this study, ST elevation almost always occurred much earlier. Coronary spasm is an attractive explanation for the observed ECG changes, especially in view of the tendency to recurrence. Another possibility is that ST elevation reflects inadequate myocardial protection during aortic cross-clamping. Because myocardial temperature was not measured, this possibility cannot be ruled out. We anticipated that inadequate myocardial protection would primarily affect the left ventricle and be evident in lead CS₅. However, some investigators have suggested that the right ventricle may be more vulnerable to ischemia than the left, because of its position in the operative field, and the proximity of relatively warm systemic venous return (7).

Regardless of the etiology of the observed ECG changes, we believe our findings have clinical implications. The ECG should be carefully reviewed during the period of reperfusion in patients undergoing coronary artery surgery, paying special attention to the inferior leads. The occurrence of ST-segment elevation should not be dismissed as an inevitable consequence of reperfusion but rather should be viewed with concern, and consideration should be given to the diagnostic possibilities mentioned earlier. Because most episodes are transient, separation from bypass should be postponed temporarily in the presence of ST-segment elevation suggesting transmural myocardial ischemia. In our experience ST elevation often

responds to elevation of coronary perfusion pressure and effective left ventricular venting. Persistent changes may respond to intracoronary nitroglycerin or calcium channel blockade. Even transient ST elevation that resolves before discontinuance of cardiopulmonary bypass should alert clinicians to an increased risk of postoperative recurrence. Further studies are indicated to confirm the retrospective findings of this study and to clarify the etiology of the observed changes.

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Postcholecystectomy Pain Relief by Intrapleural Bupivacaine in Patients with Cystic Fibrosis

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Cholecystectomy in patients with chronic lung disease is not unusual except when the patient is a young adult whose pulmonary problem is caused by cystic fibrosis (CF). Two such patients were recently treated by us. The principal concerns of the referring physicians were whether anesthesia could safely be given to these patients and whether postoperative pain control could be both safe and effective. Of these concerns, the postoperative management seemed the more vexing question. A recently described method (1) for production of analgesia by intrapleural injection of local anesthetic solution was employed successfully to solve this problem.

Report of Cases

1. A 29-year-old man was diagnosed as having CF at age 17. His height was 175 cm, weight 57 kg. He appeared ill and anxious and stated that he had been too weak to work for over a year. Significant past history included an episode of right heart failure 10 yr previously and a "nervous breakdown" 8 yr ago. Over the past 4 yr he had been admitted several times to this institution for exacerbations of his pulmonary disease and had been followed closely in our clinics. The present admission was prompted by postprandial abdominal pain. During diagnostic evaluation to discover the cause of his pain, he was given antibiotics and chest physiotherapy to improve his pulmonary status.

Physical examination revealed rales and rhonchi over both lung fields, abdominal tenderness most marked in the right upper quadrant, moderate hepatomegaly, and clubbing of his fingertips without cyanosis. An electrocardiogram and echocardiogram were normal. Pulmonary function tests (PFTs) were ab-

normal, most strikingly the maximum midexpiratory flow rate (MMEF), which was 10% of that predicted for him. The 1-sec forced vital capacity (FEV₁) was 35% of the predicted value.

Cholecystectomy was performed under general anesthesia with N₂O-O₂-isoflurane and was uneventful. The trachea was extubated in the operating room at the end of operation, after spontaneous respiration was judged to be adequate. In the recovery room, about 30 min later, he was awake and reporting pain. He was then turned on his left side and a catheter was placed in the right pleural space through an epidural needle inserted in the eighth intercostal space at the posterior axillary line. After the needle was withdrawn and the catheter was taped to his skin, 20 ml of 0.5% bupivacaine with 1:200,000 epinephrine was injected, and the patient was placed supine and flat for the next 10 min. He reported complete pain relief and was able to breathe without difficulty. Serial arterial blood gas determinations (ABGs) gave normal results. He was discharged to his room where, over the next 3 days, the same amount of the same bupivacaine solution was injected through the catheter every 8 hr. This did not satisfy the patient, who usually asked for reinjection 3 hr later, so he received modest IM doses of either meperidine (25 mg) or morphine (2 to 4 mg) on postoperative Days 1 and 2. A total of five such injections were made and after postoperative Day 2 he was given only oral acetaminophen. Recovery was uneventful.

2. A 23-year-old woman had been followed for CF at this hospital since infancy. She was 160 cm tall, weighed 37 kg, and appeared thin, anxious, but cheerful. She had no history of cor pulmonale and had no clubbing of her fingers, but PFTs revealed an FEV₁ 31% of predicted and MMEF 12% of predicted. After preoperative pulmonary preparation similar to that for the man described earlier, she was scheduled for cholecystectomy.

Operation and N₂O-O₂-isoflurane anesthesia were uneventful. An intrapleural catheter was placed in the same manner as described in the first case, except

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that it was inserted before leaving the operating room. All subsequent injections through the catheter were done in her room. The results were remarkable in that she reported 10 hr of excellent pain relief from each 20-ml injection. This more manageable schedule was followed for 3 days, then the catheter was removed. The patient was easily able to cough and deep breathe, was never sedated or depressed by these treatments, and recovered uneventfully without having been given a single injection of opioid analgesic.

Discussion

Patients with CF must live fairly long if they are to develop cholelithiasis, because biliary tract disease is not an early complication of this condition. Medical management provided by pediatricians to patients with CF has improved dramatically in recent years, so we are now confronted with new clinical problems that call for new solutions.

Salanitro et al. (2) summarized surgical and anesthetic problems during the period 1945-62 and reported a pulmonary complication rate of 60% following 135 operations performed on 93 patients with CF. Of these 93, 25 died before discharge from the hospital. A later study by Doershuk et al. (3) of 144 operations performed on 56 patients with CF between 1959 and 1970 revealed much better results. In that series, there were 20 abdominal operations but no cholecystectomies. The general principles of anesthetic management outlined by Doershuk and his colleagues are as timely today as when they were published in 1972. However, the question of postoperative analgesia was not addressed by those authors.

Pain discourages coughing and deep breathing after an upper abdominal operation. This is obviously especially hazardous in patients with severe pulmonary pathology characterized by small airway closure and tenacious secretions. One option is to ventilate these patients mechanically during the postoperative period, but this may compromise clearance of tracheobronchial secretions and may increase the likelihood of atelectasis and pneumonitis.

Rapid restoration of adequate spontaneous ventilation and extubation requires that pain relief be provided. Failure to relieve pain could set the stage for potentially fatal pulmonary complications. Opiates depress ventilation, regardless of route of administration. Epidural morphine and fentanyl have disappointed early enthusiasts as it became apparent that this route of drug delivery does not circumvent the danger of respiratory depression. Our first patient did receive intramuscular morphine in doses of 2 to 4 mg to supplement the analgesia from his intrapleural bu-

pivacaine, but there is no doubt that these nondepressant doses would have been useless as the only mode of pain relief in this patient whose tolerance to pain was minimal.

Fortunately, a new method for management of postoperative pain in patients having upper abdominal or thoracic operations has recently been introduced by Reiestad and Strømskag (1), who described the intrapleural administration of local anesthetics to 81 postoperative patients, 42 of whom had undergone cholecystectomy. Rocco et al. (4), working with Reiestad and colleagues extended these observations and noted improvement in arterial blood gas tensions after intrapleural infusion of bupivacaine. The blood levels of bupivacaine were also comfortably below toxic levels. The paper by Rocco et al. provides a clear description of this technique for relief of postoperative pain.

The mechanism of action of this treatment has not been established. Seltzer et al. (5) reported a mean maximal central venous plasma bupivacaine concentration of 2.07 $\mu\text{g/ml}$ in a group of ten patients given 30 ml of 0.5% bupivacaine with 1:100,000 epinephrine intrapleurally. Because these patients had an average of six thoracic dermatomes unilaterally insensitive to pin prick and no sign of central nervous system toxicity, it is doubtful that analgesia with this technique is due to systemic absorption of bupivacaine and subsequent central elevation of pain threshold. A far more likely explanation is retrograde diffusion of the drug through the parietal pleura, causing intercostal nerve blocks demonstrable by dermatome testing. In support of this hypothesis, a patient recently given a reinjection through an intrapleural catheter, while sitting up, developed blocks of only T10-12, of no benefit for his post-thoracotomy pain. Later, he was given another injection while lying flat in bed and had complete pain relief within 10 min, with corresponding block of higher thoracic dermatomes.

If transpleural diffusion of drug is necessary for this technique to work, pleural intravascular absorption of the agent would prevent it from reaching the intercostal nerves. The addition of epinephrine to bupivacaine should constrict pleural vessels, limit bupivacaine absorption, and thereby allow more drug to reach intercostal nerves. If more drug traverses a vasoconstricted pleura than a normal one, a more profound intercostal block should be produced. Rocco et al. (4) injected 20 ml of 0.5% bupivacaine without epinephrine and then determined that 5-10 ml/hr of this drug preparation needed to be given by continuous infusion to maintain the analgesia produced. In contrast, they found that one injection of 20 ml 0.5% bupivacaine with 1:200,000 epinephrine was effective

for 8 hr. We have used the latter technique in over 25 patients, giving the same volume of 0.5% bupivacaine with epinephrine for each injection and have not yet had a failure.

Reiestad and Strømskag (1) reported a failure in a patient with pleural fibrosis from earlier tuberculosis. They suggested that pleural thickening may cause difficulty in identifying the pleural space with this technique and thus constitute a relative contraindication to its use. Cystic fibrosis, in the absence of previous episodes of spontaneous pneumothorax, is usually not accompanied by major pleural fibrosis or adhesions that would prevent the spread of injected local anesthetic. This may not be true of other chronic pulmonary conditions, so it would be imprudent to suggest that intrapleural local anesthetic injection is the analgesic method of choice for all such patients.

The 42 cholecystectomy patients studied by Reiestad and Strømskag were presumably fairly fit, although this is not specifically stated (1). We used their technique in two cases clearly complicated by severe

pulmonary disease and the results were dramatically successful. We are confident that the difference in degree of success between the first and second patient relates to the emotional natures of these patients, not to any technical differences in the catheter placements or injections. Intrapleural analgesia was easy to achieve, caused no complications, and worked well.

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Use of Succinylcholine During Elective Pediatric Anesthesia Should Be Reevaluated

Ellise Delphin, MD, Douglas Jackson, MD, and Peter Rothstein, MD

The occurrence of a cardiac arrest during anesthesia in a child undergoing elective surgery is a rare but devastating event. Arrests due to equipment failure, human error, or misjudgment are potentially preventable by improved monitoring and training of personnel (1-3). Arrests due to the intrinsic properties of drugs or an idiosyncratic or allergic reaction to drugs used in anesthetic practice may be more difficult to prevent, as long as the drugs continue to be used.

We now present another case of a prolonged cardiac arrest after succinylcholine use in an apparently healthy child; who was later shown to have occult neuromuscular disease. We suggest that elective use of succinylcholine in pediatric anesthesia should be reevaluated.

Case Report

A 3-month-old male infant (43 weeks postconceptual age) was admitted for elective repair of a right inguinal hernia and hydrocele. The neonatal period was complicated by premature birth at 30 weeks gestation, mild respiratory distress syndrome treated with nasal CPAP for 24 hr, and episodes of apnea and bradycardia treated with theophylline for the first 3 weeks of life. He was discharged from the hospital at age 6 weeks, receiving no medication. Elective readmission for hernia repair was planned. On admission he was an active, alert infant. His weight was 4.7 kg, pulse rate 140 beats/min, respiratory rate 30 breaths/min, and blood pressure 72/40 mm Hg. Hemoglobin concentration was 11.3 g%.

He received no premedication. In the operating room, monitoring included ECG, blood pressure by automated oscillometry, heart rate and breath sounds

by precordial stethoscope, end-tidal CO₂, and pulse oximetry. Anesthesia was induced with halothane 2%, N₂O/O₂ (70%/30%) at high flows. A 22-gauge catheter was placed in the left saphenous vein. Atropine 0.1 mg was administered IV with a subsequent increase in heart rate. He was easily ventilated by mask, and oxygen saturation was continuously 100%. Succinylcholine 10 mg was administered IV to facilitate tracheal intubation. Within 30 sec he developed chest wall rigidity and limb muscle contracture. Masseter spasm was present. Intubation was accomplished rapidly with a 3.5-mm endotracheal tube. Ventilation was difficult because of poor chest wall compliance. Bradycardia, refractory to atropine administration, progressed to asystole. External cardiac massage was initiated and ventilation with 100% O₂ via the endotracheal tube was begun. His temperature, measured in the esophagus, was 36.5°C.

He remained asystolic for 8 min despite external cardiac massage, ventilation with oxygen, and administration of epinephrine, CaCl₂, NaHCO₃, and isoproterenol. He was empirically treated for hyperkalemia with glucose 5 g and insulin 0.5 U with return of spontaneous cardiac activity. He developed a slow idioventricular rhythm and then a series of ventricular dysrhythmias ranging from ventricular extrasystoles to ventricular fibrillation that were treated with lidocaine 5 mg IV, bretylium 25 mg IV, and defibrillation (10 J). He converted to a sinus tachycardia at 180 beats/min with a blood pressure of 80/50 mm Hg. Mild pulmonary edema developed. This was treated with furosemide 5 mg IV. Surgery was cancelled and he was transferred to the intensive care unit, intubated, and was given a lidocaine infusion. He was alert and moving all extremities.

In the ICU, his vital signs were stable and he was alert. Heart rate and blood pressure were normal for age. Neurologic exam revealed no focal findings. He never developed a fever. There was no recurrence of dysrhythmias.

Laboratory studies during the arrest and thereafter were remarkable for elevated CPK and potassium levels (Table 1).

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Table 1. Arterial Blood Data in an Infant After Succinylcholine-Induced Cardiac Arrest

Time	pH	PCO ₂ mm Hg	PO ₂ (F _I O ₂ 100%)	CPK (n1 = 1-50 U/L)	K ⁺ mEq/L	Comment
5 min after arrest	7.30	37	430	—	—	—
10 min after arrest	7.25	29	409	17,850	6.1	After glucose and insulin
30 min after arrest	7.35	48	587	—	—	Return of sinus rhythm; pulmonary edema
6 hr after surgery	7.38	36	500	10,360	4.9	—
24 hr after surgery	—	—	—	3510	—	—
3 days after surgery	—	—	—	1655	—	—
8 weeks after surgery	—	—	—	8000	—	—

Five days after arrest, he underwent bilateral inguinal hernia herniorrhaphies and quadriceps-muscle biopsy under general anesthesia without complication. He was given thiopental, fentanyl, pancuronium, N₂O, and O₂ using an anesthesia machine never exposed to halogenated agents. The muscle biopsy revealed grossly and microscopically damaged and necrotic muscle.

When he returned 8 weeks later for a postoperative examination, he was thriving and physical examination was normal. A repeat CPK at that time was 8000 U/L (normal 1-50 U/L). Approximately 1 year after the initial episode, muscle biopsy was performed under spinal anesthesia with tetracaine. Biopsy results were consistent with Duchenne's muscular dystrophy. The CPK before this procedure was 11,140 U/L.

Discussion

This case is presented as another example of a prolonged cardiac arrest in an apparently healthy child after the use of succinylcholine. The preoperative evaluation of this infant did not reveal any contraindication to a halothane-succinylcholine induction, a technique chosen to allow tracheal intubation without significant cardiovascular depression (4). It appears that in our patient, succinylcholine precipitated an acute muscle injury, as suggested by the increased CPK values in the perioperative period that reached values significantly greater than those seen subsequently. Cardiac arrest ensued and subsequently ventricular dysrhythmias occurred that were refractory to conventional therapy. The elevated serum potassium level obtained 10 min after the cardiac arrest and after glucose and insulin treatment suggests that the potassium level was higher at the moment of asystole. Hyperkalemia may have been a contributing or causative factor in the cardiac arrest. The significantly elevated CPK and subsequent muscle biopsy 1 year later confirmed the diagnosis of Duchenne's muscular dystrophy.

The commonly used depolarizing muscle relaxant, succinylcholine, is associated with asystole (5), bradyarrhythmias (6-8), hyperkalemia (9), masseter spasm (10-12), and malignant hyperthermia (13). Bradyarrhythmias are most often associated with repetitive doses of the drug. Hyperkalemic cardiac arrest is seen when the drug is used in patients with burns, massive muscle injury, or underlying neuromuscular disease (5). Masseter spasm has been reported in 1% of children after an inhalation induction of anesthesia with halothane followed by succinylcholine to facilitate tracheal intubation (10). On the basis of halothane-caffeine contracture tests, 50-70% of children with masseter spasm appear to be susceptible to malignant hyperthermia (11,12). There are a number of reports in the literature of prolonged cardiac arrest requiring lengthy resuscitation in apparently healthy children after use of succinylcholine. Only after the event were these children diagnosed as having underlying neuromuscular disease, usually Duchenne's muscular dystrophy (14-18).

In 1971 Ryan et al. reported the frequency of myoglobinemia to be 40% in children (prepubescent) and 4% in adults after a single IV injection of succinylcholine 1 mg/kg (19). The authors believed the data suggested "a changing response to succinylcholine that was concurrent with the onset of puberty." The myoglobinemia seemed to have few clinical implications. A comparison by Harrington et al. (20) of serum myoglobin concentrations in children receiving succinylcholine with or without halothane revealed an increase in serum myoglobin levels after succinylcholine, with the greatest elevations seen in children receiving both succinylcholine and halothane. Thus, succinylcholine, used with or without halothane, has attendant risks that could be avoided by the use of nondepolarizing drugs of intermediate duration of action.

It is not clear from this case whether halothane has a contributing role in the reaction described by ourselves and others (14-18). There is one report of a

cardiac arrest after succinylcholine in a child later shown to have muscular dystrophy who did not receive halothane (18). The data of Harrington et al. suggest that in *normal* muscle, halothane exacerbates the effects of succinylcholine that cause release of CPK (20). The same phenomenon may or may not exist in *abnormal* muscle. A definitive statement cannot be made because we do not know the mechanism of CPK release in normal or myopathic muscle.

The availability of the new intermediate-acting relaxants allows the choice of safe and efficacious agents to facilitate tracheal intubation in a population that may respond unpredictably to succinylcholine. When atracurium or vecuronium are combined with a halogenated inhalation agent, tracheal intubation can be accomplished without obliteration of all twitches as assessed by train-of-four monitoring. While these two drugs are not presently recommended by the manufacturer for infants younger than 1 month of age, we have used atracurium in neonates, without problems. Vecuronium has been reported to have a prolonged recovery time in infants, compared with children and adults, and thus might not be as appropriate a choice as atracurium (21).

In conclusion, the use of succinylcholine in elective pediatric anesthesia introduces a small but significant risk that can easily be avoided. Although the drug still has a role in a rapid sequence induction or for emergent relief of airway obstruction due to laryngospasm, we recommend that the elective use of succinylcholine in pediatric patients be reevaluated.

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Hemodynamic Changes Associated with Electroconvulsive Therapy

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Electroconvulsive therapy (ECT) is capable of provoking profound cardiovascular responses, the result of both the electroshock stimulus and the consequent seizure. Although considerable work has been performed upon ECT-induced hypertension, arrhythmias, and their consequences, no study to date has assessed the changes in cardiac output that accompany this treatment. The purpose of this study was to investigate by noninvasive means the effects of ECT on cardiac output.

Methods

Ten healthy ASA I or II patients scheduled to receive ECT were studied. The study was approved by the institutional review committee, and all patients gave informed consent. Two men and eight women were studied (mean age, 56 yr; range, 18-76). Reasons for treatment included one case of mania, two cases of schizophrenia, and seven cases of depression. No patients were receiving mood-altering drugs or drugs likely to affect the response to ECT.

Hemodynamic monitoring consisted of ECG, lead CM₅; blood pressure monitoring by the Korotkoff sound method; and cardiac output by noninvasive electrical bioimpedance (CObi) monitoring (NCCOM3, BoMed Medical Manufacturing Ltd., Irvine, CA). Electrode placement for the CObi monitor was as specified by the manufacturer; two of the four neck electrodes were positioned at the base of the neck in the frontal plane, and two were placed 5 cm caudad to these. Two of the four thoracic electrodes were positioned at the level of the xiphoid and the other two were placed 5 cm caudad to these. The device was operated in slow mode, in which the display data are updated after every 12 accepted beats.

Anesthesia consisted of consecutive injections of 6 μ g/kg atropine sulfate, 1.5 mg/kg methohexital, and

0.7 mg/kg succinylcholine. Ventilation was controlled by mask with 100% oxygen until the completion of fasciculations. An oral biteblock was then inserted and ECT performed. Controlled ventilation continued until the return of spontaneous respiration. Hemodynamic data were collected before anesthesia, at the completion of succinylcholine fasciculations, and at the completion of the convulsion. Data were analyzed by paired Student's *t*-test. The level of statistical significance used was $P < 0.05$.

Results

The mean values and standard deviations of hemodynamic variables are listed in Table 1. Induction of anesthesia was associated with a significant (13%, $P < 0.05$) decrease in cardiac output and a significant (27%, $P < 0.01$) increase in heart rate when compared with preanesthesia values. The convulsion itself was accompanied by significant increases in heart rate (20%, $P < 0.01$), blood pressure (34%, $P < 0.01$), and cardiac output (81%, $P < 0.01$) when compared with preanesthesia values.

Cardiac output increased progressively with the onset and continuation of the convulsion. All patients achieved maximal increases in cardiac output within a 30-sec period after completion of the convulsion. After this there was a return to preanesthesia cardiac output levels over the following 2 min.

With the exception of the brief period during delivery of the electroshock, function of the bioimpedance monitor was unaffected by the convulsion.

Discussion

Although remaining controversial, ECT is a widely used treatment for a narrow range of severe psychiatric disorders, primarily encompassing depressive states (1). In the United States, approximately 100,000 ECT treatments are administered annually (2).

As currently practiced, ECT is a safe procedure in which the risk entailed is not different from that associated with the use of short-acting barbiturates (1-4). There was no clear direct mortality from several large

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Table 1. Hemodynamic Variables

	Before anesthesia	After anesthesia	After convulsion
Pulse (beats/min)	81 ± 16	103 ± 12 ^a	122 ± 17 ^a
SAP ^b (mm Hg)	122 ± 15	116 ± 15	156 ± 26 ^a
CO (L·min ⁻¹)	5.5 ± 1.6	4.8 ± 1.4 ^a	8.7 ± 2.2 ^a

^a*P* < 0.05 in relation to preanesthesia values. Values are means ± SD.^bAbbreviations: SAP, systolic arterial pressure; CO, cardiac output.

recent series that together total over 35,700 treatments (5-8). Nevertheless, several hundred deaths ascribed to the treatment have been reported in the medical literature (9-13), mainly before and during the 1950s. In spite of the apparent increase in safety of the technique, isolated cases of death or severe cardiovascular complications continue to be reported (14,15). Gerring and Shields (16) reported one death in a series of 42 patients. They identified a group of patients at high risk for the development of myocardial ischemia and/or arrhythmias following ECT. This group was comprised of patients with a history of angina, myocardial infarction, congestive heart failure, arrhythmias, rheumatic heart disease, or a baseline abnormal ECG. The cardiovascular complication rate in this group was 70%.

Profound autonomic responses have been well documented as a result of both the electric shock stimulus and seizure. With the application of the stimulus, there is an initial brief period of vagal reactivity (17), followed by sympathetic hyperactivity with accompanying tachycardia and hypertension (17-19). Arrhythmias have also been widely reported (17,20,21), as well as morphologic changes of the ECG (22).

The significant increase in cardiac output with ECT, although expected, has not previously been quantitated. This is a reflection of the unreliability until recent times of noninvasive cardiac output determinations. Thoracic electrical bioimpedance (TEB) is a noninvasive continuous cardiovascular monitoring technique that estimates stroke volume on a beat-to-beat basis using an alternating current of high frequency and low magnitude is applied to the thorax (23-27).

The dramatic increase in cardiac output that accompanies ECT resolved over 2-3 min after termination of the convulsion. It is not surprising that serious cardiovascular problems may arise in the type of high-risk patient described by Gerring and Shields (16). Such problems, although infrequent, arise as a result of a treatment process that, as well as increasing oxygen demand (28), has the potential to profoundly affect the autonomic nervous system.

In summary, the cardiovascular response to the induction of anesthesia and subsequent ECT were studied noninvasively in ten healthy patients. Induction of anesthesia was associated with a 13% decrease in cardiac output and a 27% increase in heart rate. The convulsion itself was accompanied by a 20% increase in heart rate (*P* < 0.01), 34% increase in blood pressure (*P* < 0.01), and 81% increase in cardiac output (*P* < 0.01) when compared with preanesthesia values. The authors conclude that a hyperdynamic cardiovascular state occurs with the convulsion brought about by ECT. These hemodynamic damages could have significance in patients with underlying cardiovascular disease.

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Letters to the Editor

Midazolam and Cimetidine: Lack of Interaction is Unproven

To the Editor:

The paper by Greenblatt et al. (1) is at odds with previously published work on this subject by Klotz, et al. (2) who described significant alterations in midazolam pharmacokinetics when administering cimetidine to subjects with constant plasma levels of midazolam. The difference between the papers by Greenblatt et al. (1) and Klotz et al. (2) can be explained by the fact that in the formers' study, plasma cimetidine concentrations for 24 hr after the intravenous administration of midazolam were subtherapeutic.

Somogyi et al. (3) found the mean therapeutic plasma concentration of cimetidine to be 1.0 $\mu\text{g/ml}$ with a range of 0.64 to 1.64 $\mu\text{g/ml}$ on a daily dose of 1000 mg cimetidine. In Greenblatt's study (1), the mean plasma cimetidine concentration for the 24-hr period was 0.54 $\mu\text{g/ml}$, despite the authors' statement that a concentration of 0.61 $\mu\text{g/ml}$ was achieved. In the study by Klotz et al. (2), the plasma level of cimetidine averaged 2.53 $\mu\text{g/ml}$. Thus, the finding by Greenblatt et al. (1) cannot be used to infer that there is no interaction between midazolam and cimetidine, because plasma levels of cimetidine were not in the clinically effective range. The possibility of an interaction between midazolam and cimetidine is obviously important in the intensive care unit when simultaneously using midazolam for sedation and cimetidine for stress ulcer prophylaxis.

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Pitfalls Encountered in Relating Anterior Fontanel Pressure to Intracranial Pressure

To the Editor:

Readers of the paper by Friesen and Thieme (1) describing changes in anterior fontanel pressure during cardiopulmonary bypass and hypothermic circulatory arrest in infants, should be aware of the controversy concerning the relation between anterior fontanel pressure (AFP) and intracranial pressure (ICP). The authors appear to have been misled by the overly optimistic reports by Vidyasagar and Raju, Myerberg et al., and Hill and Volpe with regard to the accuracy of AFP measurements using the Ladd monitoring system (2-4). Although the Ladd sensor is certainly an excellent, highly accurate and reliable device, the method of attachment of the sensor to the fontanel presents problems. Reports by the previously mentioned investigators (2-4) indicate that application force (the pressure the adhesive foam applies to the sensor) has no effect on AFP measurements. However, this conclusion is not in agreement with reports by Walsh and Logan and Horbar et al., who indicate substantial variation in AFP with application pressure (5,6). In studies in which correlation between AFP and ICP are claimed, it appears that the sensor was applied with prior knowledge of the CSF pressure measured from some "invasive source". No correlation between AFP measured after "blind application" and CSF pressure has yet been adequately demonstrated with the fiberoptic sensor.

Our investigation (7) into the AFP and ICP indicated that accurate correlation of AFP and ICP requires that three conditions be met. First, the sensor applied to the fontanel must have a base of sufficient diameter so that its outer edges rest on the area beyond the anterior fontanel membrane-cranial bone interface. This provides a consistent and stable reference from which pressure measurements can be made. Sensors having smaller cross-sectional base diameters than the smallest dimension of the anterior fontanel tend to "float" on the fontanel and their output (AFP) therefore depends on the extent to which the application device presses it into the fontanel window. Because the Ladd sensor is 10 mm in diameter, it is not unreasonable to expect application force

to affect its output. Second, given sufficient sensor base diameter, it is necessary for the attachment device to apply enough pressure to the sensor to ensure that the sensor base contacts the fontanel cranial bone margin. Bench studies on infant cranial models in our laboratories suggest that application pressures sufficient to bring the sensor base in contact with fontanel-cranial bone margin slightly exceed the ICP (7). Third, the application of fontanel sensors with adhesive foam or tape may be useful for short-duration monitoring only, because of the significant drift that is observed in the sensor output with time. Adhesives tend to slip over time and, in combination with gradual material relaxation (stretching), invariably lead to lower estimates of AFP (7). Hill and Volpe also indicate that reapplication of the sensor was necessary after 1-2 hr when attached with adhesive foam (4). Therefore, it is essential that the sensor application method avoid these problems if accurate measurements of and correlations between AFP and ICP are to be obtained.

Although the relative changes described by Friesen and Thieme may be reasonably accurate, when using the Ladd sensor as described in their article the absolute values for AFP may not necessarily correlate to the actual ICP.

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In Response:

It takes the first-time user of the Ladd monitor (Ladd Research Industries, Inc., Burlington, VT) only a few minutes to realize that application force affects anterior fontanel pressure (AFP) measurements. We, too, are well aware of that fact, and the text of our paper (1) clearly reflects that awareness with reference to the same reports that Bunegin and Albin cite (2,3).

Because the technique of application of the sensor to the anterior fontanel is so important, we chose to use the technique described by Hill and Volpe (4). Contrary to the state-

ment in Bunegin and Albin's letter, Hill and Volpe did recognize the problem of application force. In fact, that is why they developed and studied their application technique, which they demonstrated to be reproducible and to correlate well with directly measured intracranial pressure (ICP) (4). There is nothing in Hill and Volpe's article—or in the other two referred to by Bunegin and Albin (5,6)—to support the allegation that the AFP sensor was applied with prior knowledge of directly measured ICP.

We have not had the opportunity to read Bunegin and Albin's investigation of AFP monitoring (7) because it was still in press at the time of this correspondence. However, it appears (through reading their letter) that their work may explain why Hill and Volpe's application technique is reliable and accurate. The sensor is held in place by a piece of adhesive foam (Reston, 3M Company, St. Paul, MN) of greater diameter than the fontanel. The foam overlaps the bony edges of the fontanel and the sensor adheres to the sticky underside of the foam. Thus, while the sensor maintains adequate contact with the fontanel, its position is fixed in relation to the cranium and it does not tend to "float" on the fontanel.

We have not used the Ladd monitor for prolonged periods of time, so are unable to comment on the occurrence of stretching (gradual material relaxation) of the foam during its use.

Finally, Bunegin and Albin express concern that measured AFP values not be equated with absolute ICP. We certainly agree and think it unfortunate that many of the articles in the literature dealing with this topic use the terms AFP and ICP interchangeably. We have not used AFP and ICP interchangeably and have not assigned numeric values to ICP in our investigations using the Ladd monitor. However, properly measured AFP does correlate well with ICP, and we think that conclusions drawn from studies of AFP can be generally applied to ICP with validity.

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The First Reported Oral Intubation of the Human Trachea

To the Editor:

The authors of the interesting article "Esophageal intubation: A review of Detection Techniques" (1) start with the statement that the first human orotracheal intubation was performed in 1878. I feel as a historically interested anesthetist that a correction is in order.

It is true that the first orotracheal intubation for anesthesia was performed in 1878 by William Macewen, 10 years after the description of the technique of endotracheal anesthesia with the help of a tracheotomy tube by the surgeon Friedrich Trendelenburg (2). However, the first report of orotracheal intubation of the human trachea was more than 800 years before either of these.

It is now generally accepted that the famous Arabian physician Avicenna (980-1037) described in about the year 1000 in his medical work "Liber Canonis" the orotracheal intubation with the following in Latin: "Et quandoque intromittitur in gutture cannula facta de auro aut argento aut similibus ambobus, adjuvando ad inspirandum" (3).

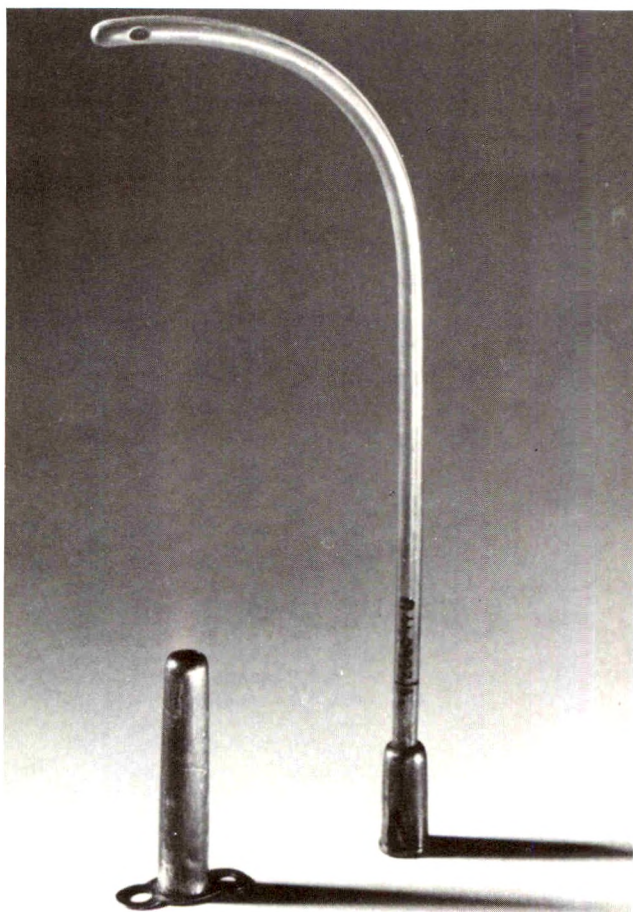


Figure 1. A metal endotracheal tube (right), shaped like a male catheter, for orotracheal intubation. Such a tube has been described by Charles Kite in his "Essay on the Recovery of the Apparently Dead" (With friendly permission of the Wellcome Museum for the History of Medicine, London).

At that time the expression "guttur" meant "throat" (4); a liberal translation is the following: "When necessary, a cannula of gold, silver, or another suitable material is advanced down the 'throat' to support inspiration."

In addition, in the 18th century, the Age of Rationalism, the technique of orotracheal intubation became an essential part of resuscitation methods, especially in drowned persons. The English physician Charles Kite, for example, wrote in his monograph "An Essay on the Recovery of the Apparently Dead" (5) the following:

"If any difficulty should arise in distending the lungs, it must proceed either from water in the windpipe, or a contraction or adhesion of the epiglottis. We have already pointed out the method of discovering when the first circumstance occurs; and when the latter is the case, we shall generally remedy the inconvenience by bringing the tongue forwards, which, being connected to the epiglottis by inelastic liga-

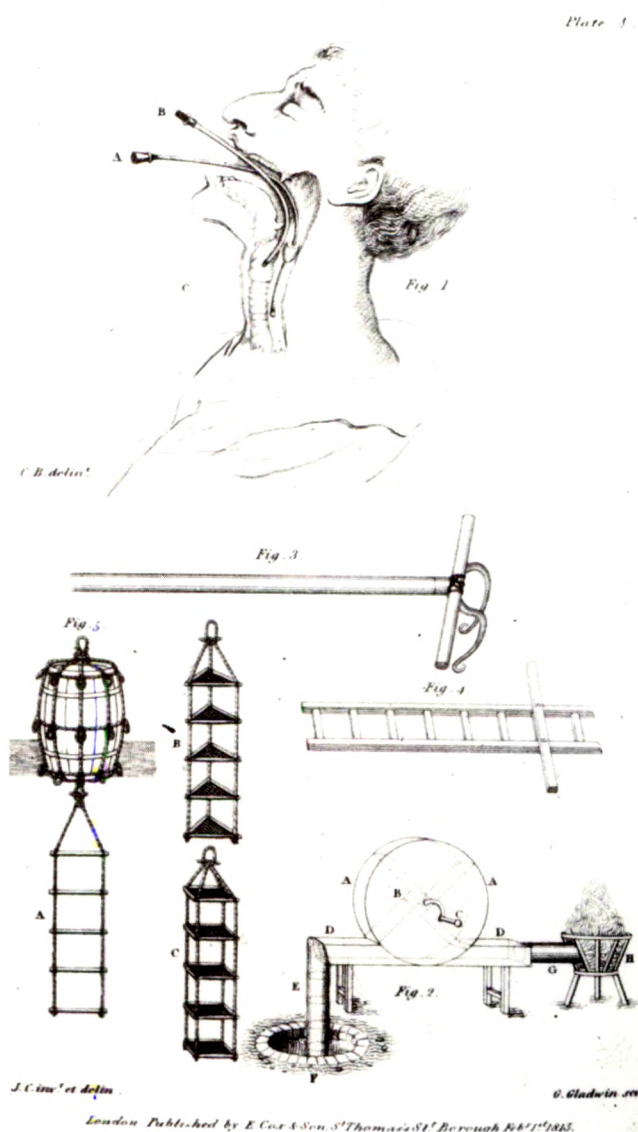


Figure 2. Plate 4 in James Curry's monograph "Observations on Apparent Death." The upper part of the plate shows an orotracheal intubation with a curved metal tube similar to the tube in Figure 1.

ments, must of course be elevated. *Should any further impediment however occur, the crooked tube, bent like a male catheter, recommended by Dr. Monro, and mentioned by Mr. Portal, Mr. le Cat and others, should be introduced into the glottis, through the mouth or one nostril; the end should be connected to a blow pipe, . . .*"

Figure 1 shows the tube described by Kite (with permission of The Wellcome Museum for the History of Medicine, London). Twenty-seven years after Kite's description of orotracheal intubation technique, we find the first illustration of an orotracheal intubation in the medical literature (Fig. 2) when James Curry from Edinburgh, Scotland, illustrated orotracheal and esophageal intubation in his monograph "Observations on Apparent Death" (6).

In conclusion, although William Macewen was the first to introduce the technique into anesthesia, oral intubation was known hundreds of years before.

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Safe Placement of the Long-Arm CVP

To the Editor:

Long (60-cm) Intracath "through the needle" catheters (Deseret Medical, Inc.) are frequently placed as central venous lines via an antecubital vein in major head and neck cases, including sitting position craniotomies. However, failure to advance the tip of the catheter to an intrathoracic position is not uncommon. This failure may be because the bevel of the large 14-gauge introducer needle is not entirely within the vein. Even when the catheter has been properly introduced into the vessel, further manipulation in attempting to thread the catheter centrally through valves and bifurcations is made difficult and even hazardous because of the tendency of the catheter to catch on the sharp needle bevel, shear off, and possibly embolize.

We have found that the Intracath with its wire stylet in place can be threaded through a 14-gauge "over the needle" catheter (e.g., 14-gauge Cathlon IVTM by Critikon) after

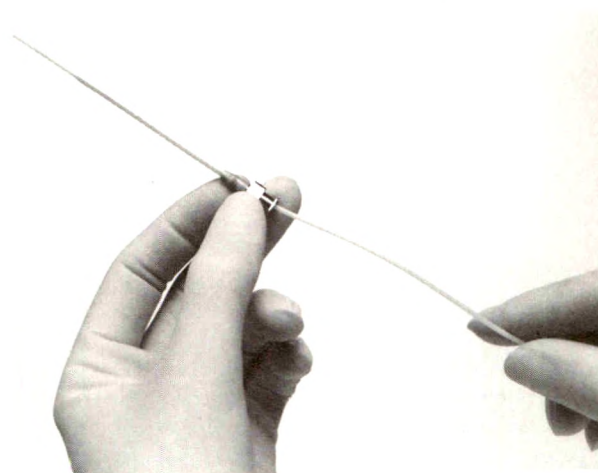


Figure 1. The Intracath slides easily through the 14-gauge intra-venous catheter.

removal of the needle (Fig. 1). The flexible Cathlon catheter will not shear the Intracath. Manipulations to achieve central placement can thus be done with greater safety. In addition, the hub of the Intracath fits snugly into the hub of the Cathlon.

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Anterior Approach to Sciatic Nerve Block in Children: Loss of Resistance or Nerve Stimulator for Identifying the Neurovascular Compartment

To the Editor:

I have previously reported on a series of children who had sciatic nerve blocks using the anterior approach (1). I used a modification of the loss of resistance (LOR) technique initially commented on by Beck (2) and by Magora et al. (3). Although this technique appears to be efficient, it might be that it is not such an efficient method of placing the needle point in the neurovascular compartment as the use of a nerve stimulator, as advocated by Brown (4). Consequently, I devised a study to determine whether it is only necessary that the needle point be in the compartment, or whether it must be near enough the nerve to elicit a response following electrical stimulation.

Forty-two blocks were undertaken in 39 children as shown in Table 1. Premedication consisted of droperidol and diazepam, 200 µg/kg of each orally. Anesthesia was induced with thiopental, 3-5 mg/kg, or N₂O, O₂, and halothane, and maintained with N₂O, O₂ and halothane. No muscle



Table 1. Details of Patients in the Study

Age range (yr) (mean)	Weight range (kg) (mean)	Operative Procedures			
		TAL	STC	Osteo	Others
$\frac{1}{2}$ –15 $\frac{1}{2}$ (5 $\frac{1}{2}$)	7.5–45 (20.9)	18	16	5	3

Abbreviations: TAL, tendo-achilles lengthening; STC, soft tissue correction; Osteo, osteotomies.

Forty-two blocks performed on 39 patients. (Forty successful blocks in 37 patients.)

relaxants were used during stimulation of the nerve, and no children received pre- or intraoperative analgesia apart from the blocks. The sciatic neurovascular compartment was identified by LOR using an uninsulated 18-gauge, 9-cm spinal needle attached to a syringe of bupivacaine 0.5%. A nerve stimulator with the current set according to Kempthorne and Brown (5) was then attached to the patient and pulsed once per second. The foot was observed for evidence of sciatic nerve stimulation.

Blocks were assessed postoperatively by recovery and ward nursing staff. Two blocks failed, and these patients required immediate opiate analgesia. The 37 patients with successful blocks all showed stimulation of the thigh muscles, but only two showed any evidence of sciatic nerve stimulation.

This may be due to the needle point only being in the neurovascular compartment but not near the nerve, thereby providing a degree of safety with the LOR technique. Indeed, in order for maximal electrical stimulation to take place the needle point may actually have to pass beyond the nerve, for although Montgomery et al. (6) considered that the maximum current density was at the tip of uninsulated needles, Bashein et al. (7) and Ford et al. (8) have suggested that the maximum current density is not at the needle point but 0.5–1.0 cm proximal to it.

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Hypotension during Carotid Endarterectomy

To the Editor:

Hypotension should obviously be avoided during carotid endarterectomy. However, the etiology of the hypotension needs to be quickly identified to correct the problem.

I recently administered anesthesia to a 74-yr-old man who was having a right carotid endarterectomy performed under general anesthesia. The right carotid artery was cross-clamped by the surgeon, at which time I noticed that the blood pressure, which was recorded by a right radial arterial line, was unchanged. The hemoglobin saturation remained at 100% (Nellcor oximeter, left index finger), the ECG was unchanged, and the power spectrum analyzer (PSA-Neurologics) recorded a power level above preinduction level. The surgeon placed a Pruitt-Inahara shunt in the right carotid artery. At this time the arterial waveform became severely damped. Attempts to correct the waveform by flexing the wrist (both arms were tucked at the patient's side) and flushing the catheter were unsuccessful. The Dinamap (right arm) confirmed the arterial line recorded blood pressure of 70/30. What puzzled me at the time was that the oximeter, PSA, and ECG were unchanged despite the hypotension.

All attempts to increase the blood pressure were unsuccessful. After the endarterectomy (about 15 min) was performed, the shunt was removed and the arterial line waveform returned, revealing hypertension.

Obviously what had happened was that a portion of the proximal end of the shunt had been placed in the right innominate artery. The balloon was inflated, which severely restricted blood flow to the right upper extremity.

I describe this case to make everyone aware of this situation. The excitement of a potential disaster often can make one not think of the obvious. I now place the Dinamap or my own blood pressure cuff on the contralateral arm to the arterial line.

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Intermittent Oxygen Delivery in an Ohmeda Unitrol Anesthesia Machine Due to a Faulty O-Ring Check Valve Assembly

To the Editor:

Failures in oxygen delivery systems in anesthesia machines have been reported previously (1–6). We recently encountered an unusual variation of this problem.

Essential to the oxygen pipeline inlet in the Ohmeda Unitrol anesthesia machine is an oxygen check valve, which

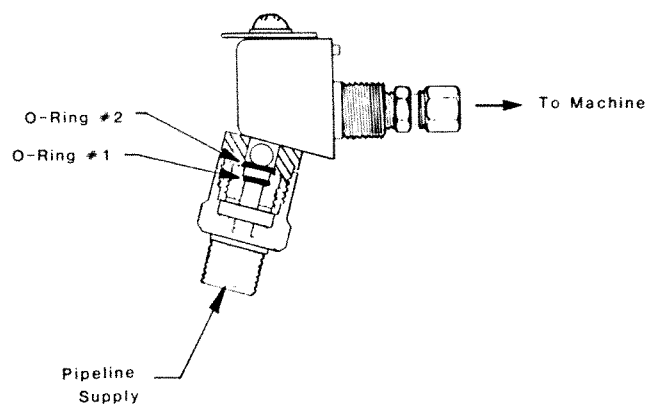


Figure 1. Check valve assembly with O-rings and ball for the oxygen pipeline inlet of the Ohmeda Unitrol anesthesia machine.

prevents escape of cylinder gases to either the hospital pipeline system or the atmosphere (7). In an apparent effort to standardize check valves among their machines, Ohmeda introduced a new check valve assembly consisting of a ball and two rubber "O" rings (Figs. 1 and 2) into some Unitrol machines in 1984.

On initial use of four new machines delivered in 1985, we observed that, once the oxygen pipeline was connected and the oxygen turned on, the oxygen bobbin would hesitate for several seconds. Although annoying, this problem did not seem dangerous to patients until an intermittent failure in the oxygen delivery system caused oxygen flow to cease. The oxygen flow bobbin fell after the oxygen flush valve had been used. No sustained hypoxia occurred because oxygen monitors detected the problem and it was corrected.

After conferring with representatives of Ohmeda, we offer the following explanation of this important problem. When the oxygen flush was used, the ball passed through O-ring #2 and became lodged against O-ring #1 (Fig. 2). Pipeline pressure, for unknown reasons, did not force the ball back through O-ring #2 into its proper position, and oxygen flow to the machine was obstructed by the ball. Because the pipeline pressure gauge was placed before the check valve in the gas flow sequence, the gauge registered pipeline pressure, even though oxygen did not flow past the check valve. Use of the flush valve system downstream from the check valve assembly apparently caused pressure to increase temporarily, which kept the ball lodged against O-ring #1. Once the flushing was discontinued, pipeline pressure sometimes would prevent the ball from returning to its proper position. Temporary disconnection from the pipeline oxygen supply would allow the ball to reseat, which restored proper function.

The problem of intermittent oxygen delivery was resolved by removing the O-ring. A "chattering" noise was created, however, presumably by movement of the metal ball due to fluctuating pressure in the oxygen inlet check valve. Replacement of the altered assembly with a bullet-like valve eliminated both the chatter and the potential for

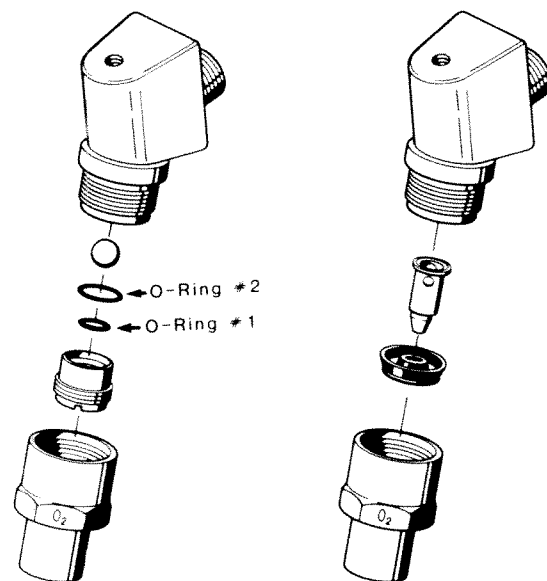


Figure 2. LEFT, ABOVE: Arrangement of O-rings and ball of check valve assembly, which malfunctioned.

Figure 3. RIGHT, ABOVE: A bullet-like valve prevents the obstruction of gas flow created by O-rings and a ball.

intermittent obstruction of oxygen flow (Fig. 3). The manufacturer has been made aware of the problem.

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Preoperative Ranitidine and Metoclopramide

To the Editor:

The Clinical Report by Manchikanti et al. (1) assesses the effects of various modes of premedication on acid aspiration pneumonitis risk factors in outpatient surgery; the study demonstrated that patients receiving no premedication, meperidine IM or IV, diazepam IV or PO with hydroxyzine IM or PO, or prochlorperazine IV had similar gastric volumes and pH levels. Because a significant proportion of the patients had a gastric pH of <2.5 and a gastric volume of >25 ml, the authors conclude that drugs used to favorably alter gastric contents will be an adjunct to safe anesthetic practice. In addition to those four preanesthetic medication regimens reviewed in his article, other preanesthetic regimens have been evaluated, i.e., glycopyrrolate and cimetidine (2), ranitidine (3), sodium citrate and metoclopramide (4).

Because several anesthesiologists here commonly order a combination of ranitidine and metoclopramide preoperatively, we decided to assess the efficacy of the regimen. Fifty consecutive ASA class I or II women (age 33 ± 4.2 yr; height 165.1 ± 5.0 cm; weight 69.7 ± 13.0 kg; mean $\pm$ SD) scheduled for outpatient laparoscopic surgical procedures were given written instructions and medication at the time of the gynecologic office visit before the surgical procedure. If not allergic to these medications, the patients were instructed to take 150 mg ranitidine with a sip of water at bedtime on the night before surgery. Ranitidine 150 mg and metoclopramide 10 mg were then both taken orally with a sip of water before leaving for the hospital. After induction of anesthesia and tracheal intubation, a gastric tube was placed for removal of gastric contents. Time from ingestion of medication to sampling averaged 153 ± 48 minutes. The gastric volume averaged 6.41 ± 3.7 ml, pH 6.07 ± 1.06 . Of interest is that no patient had a gastric pH <3.5 or a volume >15 ml. (Three patients who failed to take the medication had gastric contents with an average pH of $1.23 \pm .20$ and volume of 30.3 ± 3.2 ml). The averages we observed in this study are similar to those reported by Maltby et al. (5) when ranitidine alone was given; however, none of our patients given ranitidine and metoclopramide had a gastric pH of <3.5 , whereas 7% of those given ranitidine and 150 ml water and 13% of those given ranitidine alone by Maltby et al. had a gastric pH of 2.5 or less. Still, none of the patients in the study by Maltby et al. who were given ranitidine alone had a gastric volume of >25 ml.

An interesting finding associated with our study was that of minimal degree of postanesthetic nausea (average less than 1 on a 1 to 10 scale) and vomiting (one patient vomited approximately 5 ml). This may be related to a central antiemetic action of the metoclopramide and/or very low gastric volumes, although a larger study would be necessary to produce statistically significant numbers to prove the validity of our findings.

From our small study it seems that the combination of oral ranitidine and metoclopramide provides maximal pro-

tection from gastric aspiration pneumonitis risk factors and does so with 1) no cost to outpatient surgical efficiency because no nursing time is required; 2) no patient discomfort because medications are given orally; 3) minimal pharmaceutical cost (\$2.30); and 4) a system of medication delivery quite feasible for an active private practice.

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Stretching with Obstruction of an Epidural Catheter

To the Editor:

We recently encountered an interesting cause of difficulty in injecting anesthetic solution through an epidural catheter. An ASA class III patient had combined epidural/general anesthesia for a 3-hr exploratory laparotomy and nephrectomy. Before surgery, a Portex 19-gauge, clear nylon, non-radio-opaque epidural catheter was placed at the L2-L3 level without difficulty. Local anesthetic injected through the catheter gave a T6 sensory level. General anesthesia was then induced and maintained. During surgery, local anesthetic was intermittently injected through the catheter without difficulty. On attempting to inject morphine solution through the catheter in the recovery room to relieve postoperative pain, we found resistance so great we were unable to inject any fluid. When we untaped the epidural catheter, which was still securely taped onto the patient's back and left shoulder, we found a 4-cm segment of thinly stretched catheter where it had been taped on the patient's back. This stretching of the catheter had produced total occlusion of the lumen. The catheter distal to the stretched portion was cleansed, cut, and reattached to the catheter connector. Morphine (5 mg in 10 ml) was then injected through the catheter with no difficulty and adequate analgesia was obtained.

A search of the literature revealed reports of difficulties in removing epidural catheters (1,2), kinking of epidural

catheters (3), and shearing of epidural catheters (4,5), but no report of obstruction of a stretched epidural catheter due to stretching. We postulated that in moving the patient from the operating room table to the recovery room bed, the taped catheter became stretched. If difficulty is encountered in injecting an epidural catheter, this case suggests that catheter lumen patency should also be checked.

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Effect of Alkalinization on the pH of Local Anesthetic Solutions

To the Editor:

The adjustment of the pH of local anesthetic solutions toward the physiologic range produces more rapid onset of analgesia and surgical anesthesia by making more of the base form of the anesthetic available to diffuse across the nerve membrane (1). We recently measured the pH of various local anesthetic solutions to which increments of sodium bicarbonate were added. Although some of this material has been reported previously (2,3) the purpose of this letter is to present the data we obtained, and to summarize this information in a single report together with some new data.

Commercial preparations of plain and epinephrine-containing solutions were used and compared with plain solutions to which epinephrine (1:200,000) was added as a fresh preparation. The anesthetic solutions were drawn from the commercial containers and placed in a clean, dry, 30-ml, glass beaker. The pH of the solutions was determined using a Corning model 10 pH Meter. Sodium bicarbonate (Abbott Labs, 8.4%, 1 mEq/ml) was slowly added to the anesthetic solution and thoroughly mixed by continuous swirling of the beaker. The amount of sodium bicarbonate added to each of the anesthetic solutions is based on common clinical practice where appropriate and listed in the notation at the end of Table 1. The pH of 8.4% NaHCO_3 is 8.5.

We would like to express our appreciation to Dr. Cosmo

Table 1. pH of Local Anesthetic Solutions

Anesthetic agent	Commercial preparation	Epinephrine added	Bicarbonate added
1.5% lidocaine (Astra)	6.35	6.33	7.35 ^a
1.5% lidocaine with epi. 1:200,000 (Astra)	4.16	—	7.15 ^a
1.5% mepivacaine (Winthrop-Breon)	5.31*	5.27*	7.20 ^{a,*} (6.90) ^b
0.5% bupivacaine (Astra)	6.04	5.99	7.10 ^{a,p} (6.99) ^d
0.5% bupivacaine with epi. 1:200,000 (Winthrop-Breon)	3.73	—	5.30 ^a
3% 2-chloroprocaine (Astra)	3.89	—	7.40 ^a (6.88) ^b

Three samples of each preparation were analyzed and the reported pH represents the means of the values obtained. These results generally agree with the data from other investigations.

*New data.

^a1 mEq NaHCO_3 /10-ml anesthetic solution.

^b1 mEq NaHCO_3 /30-ml anesthetic solution.

^c0.1 mEq NaHCO_3 /10-ml anesthetic solution.

^d0.1 mEq NaHCO_3 /20-ml anesthetic solution.

^pIndicates precipitate formation upon alkalinization of the solution.

DiFazio, who initiated our interest in this subject.

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Inexpensive Heart Rate Monitor for Epidural Test Doses

To the Editor:

It has been recommended that local anesthetic solutions containing epinephrine be used for test doses to detect intravascular injection in the performance of epidural anesthesia. Accurate measurement of heart rate is, of course, essential. A finger on the pulse is inexpensive, but is not practical when wearing sterile gloves. An electrocardiographic monitor may be used, but it requires considerable space, and costs upwards of \$700 for the monitor plus per-

haps two or three electrode pads at 35¢ or more each. Pulse oximeters may be useful, but again at significant cost for the basic unit.

We have tried and are using an inexpensive device for pulse monitoring. The Sears model 564-291520 pulse monitor is intended as a heart rate monitor for use with exercising. It is small, measuring $2.3 \times 11.1 \times 6.4$ cm exclusive of the earpiece sensor; it fits readily into a pocket, and is battery powered. A photoelectric sensor detects the pulse and produces a nearly beat-to-beat readout of the heart rate on a small LCD screen. The sensor is applied comfortably to an earlobe before the induction of epidural anesthesia, and is left in place for several minutes after the test dose and initial anesthetizing dose have been injected. Comparison with ECG heart rates showed correlation within one to three beats. Because the monitor requires no special electrodes and costs \$99.95, it presents an inexpensive, portable, ready means of heart rate monitoring that we have found to be very useful and adequately sensitive and accurate for our purposes.

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Ketamine Anesthesia in Dogs Undergoing Liver Transplantation

To the Editor:

We read with interest the study of DeWolf et al. of glucose metabolism during liver transplantation in dogs (1). We are particularly interested in how the authors determined that the intravenous ketamine dose used ("2 mg/kg followed by 1 mg/kg every 20–30 min") was sufficient to render the animals insensitive to the noxious stimulation of abdominal surgery. We realize that intravenous ketamine 2 mg/kg is a commonly used anesthetic induction dose in humans. However, our clinical experience indicates that intravenous ketamine 2 mg/kg administered to nonparalyzed healthy dogs does not abolish vocalization or gross movement in response to a noxious stimulus (tail or toe pinch with forceps). Pharmacokinetic data also suggest that the maintenance ketamine doses administered in the study were inappropriate for dogs. Initial redistribution half-life ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$) of intravenous ketamine in humans are reported to be 7 to 11 min and 2 to 3 hr, respectively (2,3). Published values for $t_{1/2\alpha}$ and $t_{1/2\beta}$ in dogs are approximately 2 minutes and 61 minutes, respectively (4). Inadequate anesthesia or analgesia in healthy dogs given ketamine and pancuronium may result in increased blood pressure and heart rate in response to surgical stimulus in the preanhepatic (prebypass) period. However, hemodynamic data were not reported in the study of DeWolf et al. (1).

The authors reported that hypoglycemia did not occur

in their dogs and that blood glucagon levels increased intraoperatively. Stress due to inadequate anesthesia or analgesia could increase blood glucagon, glucocorticoid and epinephrine levels, resulting in gluconeogenesis, glycogenolysis and inhibition of glucose utilization.

The authors included hyperkalemia as one of the changes during reperfusion that were similar to results in human liver transplantation. However, data reported in their study indicate that the dogs were not hyperkalemic. The mean K^+ concentrations of 2.63 and 2.87 mEq/L in the preanhepatic stage are below published normal values for dogs (5,6). The mean K^+ concentrations of 4.10 and 3.30 mEq/L in the postanhepatic stage are within normal limits and below normal, respectively, compared to published values (5,6). We consider hypokalemia unusual in the stage I preanhepatic phase of surgery in animals that presumably were normal healthy dogs before they were anesthetized. Assuming they were normal dogs, we suspect that the hypokalemia could be related to anesthetic management. Intravenous epinephrine infusion in humans and laboratory dogs is associated with reduction of plasma K^+ levels and can result in hypokalemia (7,8). Endogenous plasma epinephrine levels may be elevated during inadequate surgical anesthesia; however, we do not know if hypokalemia is associated with conditions of severe pain or stress.

We also note that while end-tidal CO_2 was maintained between 4 and 5%, mean arterial PCO_2 ranged from 24.6 to 29.3 mm Hg, with a maximal SEM of 2.0 mm Hg (1). This discrepancy is qualitatively inappropriate, because end-tidal PCO_2 should be less than arterial PCO_2 . We wonder what explanation the authors have for this.

In summary, we suggest that some of the metabolic variables studied by DeWolf et al. may have been significantly influenced by their anesthetic technique, which, in our opinion, may have been inadequate. Moreover, we are concerned that future experiments involving major surgery in dogs will employ the same anesthetic technique. We strongly suggest reevaluation of the ketamine dose used by DeWolf et al.

We also suggest that neuromuscular blocking agents not be used as adjuncts in anesthetizing animals for surgery, unless the investigator has evidence for the efficacy of the dose of anesthetic or analgesic drug administered. Wide variation often exists between laboratory species in the effect and disposition of pharmacological agents. A drug dosage useful in anesthetizing individuals of one species may be inadequate or toxic for another species.

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In Response:

In response to the letter from Drs. Wong and Haskins regarding the adequacy of anesthesia in the dogs in our study, we regret that there is an error in our report. Although the text states that "anesthesia was induced and maintained with intravenous ketamine (2 mg/kg followed by 1 mg/kg every 20-30 minutes)," in fact anesthesia was induced with sodium thiopental (25 mg/kg IV). Shortly after induction, animals also received pancuronium 0.1 mg/kg. Thereafter, anesthesia was maintained with intravenous ketamine (2-5 mg/kg), at frequent intervals guided by indications of sym-

pathetic stimulation. Some animals, in addition, received intermittent boluses of sodium thiopental (50 mg IV). To avoid postoperative muscle weakness, few animals received any additional muscle relaxant. Therefore, except for the first hour after the beginning of the experiments, most animals were not paralyzed and would have moved in response to a perceived surgical stimulus. Thus, the dose of anesthetic was titrated according to clinical signs, as is the case in humans, and was adequate.

We agree that P_{aCO_2} was commonly lower than 30 mm Hg, but this was clearly not in response to noxious stimuli; all animals were mechanically ventilated and hyperventilation was sometimes used to counteract metabolic acidosis and to maintain pH in the normal range.

In summary, we erred in our report, markedly understating the types and amount of anesthesia used. We apologize for the error. We believe that the animals in our study did not receive inadequate amounts of anesthesia.

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Book Review

Anesthesia, the Heart and the Vascular System
T.H. Stanley and W.C. Petty, eds., The Netherlands:
Martinus Nijhoff, 1987, 226 pp, \$62.00.

I always enjoy reading small, meaty books, so I was very happy when asked to review this half-inch-thick, 226-page book. It contains the Refresher Course manuscripts of the 32nd Annual Postgraduate Course in Anesthesiology, which took place in Salt Lake City on February 20-24, 1987. Therefore, it represents the up-to-date thinking of 12 academic cardiovascular anesthesiologists (and one veterinarian) on various subjects of interest to those of us who deal with patients with cardiac or vascular disease.

To quote from the preface, the purposes of the book are to serve as a reference for the anesthesiologists attending the meeting and to serve as a vehicle to bring many of the latest concepts in anesthesiology to others within a short time of the formal presentation.

The book contains 26 submitted essays by 13 authors. The essays average eight pages each and are, in general, well written, cogent, and well referenced. The two extremes are a 2-page, non-referenced essay on The Cardiovascular Effects of Anesthetics in the Young, and a 28-page, scholarly essay with 82 references on Mechanisms and Management of Cardiac Arrhythmias.

The bad news is the price of the book (\$62.00). Compared to the ASA Refresher Course Booklets, which are also timely and written in a similar style and yet sell for \$15.00 or less, this book is grossly overpriced. Perhaps the publishers could cut the cost by soft instead of hard binding. The pricing is difficult to understand because the book was not typeset (it has obviously varying typefaces and line spacing throughout).

In summary, I enjoyed reading the book and found it to be a valuable quick review of current thinking in cardiovascular anesthesia. However, I got the book for free. I would recommend it to those who need an income tax deduction as well as a good review of cardiovascular anesthesia.

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Practical Aspects of Blood Administration
A.W. Reynolds, D. Steckler, eds., Arlington, VA:
American Association of Blood Banks, 1986, 105 pp,
\$19.00.

This slim volume meets the needs of the medical students and beginning residents in surgery and anesthesia. There is a wealth of information useful to the emergency room, operating room, and patient care areas.

This book is meant to be an interface text between phlebotomists, blood bankers, and transfusionists. As such, it does an admirable job in the tradition of the series of workshop publications published by the American Society of Blood Bankers. It deals with important questions on technical aspects of blood transfusion including needle size, filter size, and choice of an administration set. Although the use of microaggregate filters is discussed, I could find no mention of their use in preventing transfusion-associated febrile reactions. Findings since 1983 suggest that the use of microaggregate filters can reduce the incidence of these problems.

The book covers practical applications of blood product administration, replacement, hemostasis, and neutropenia. It emphasizes that the blood supply in the United States is derived from volunteer services. The book highlights problems of infection transmission through blood products, and notes the similarity between distribution of hepatitis and human immunodeficiency virus (HIV) in regional donor populations. Directed donations are mentioned, and the absence of data supporting the superiority of directed donations over regular homologous blood is emphasized. The need to inform patients on the availability of autologous predeposit programs is discussed.

The book provides a brief outline on the management of patients whose religious beliefs prevent them from accepting blood products. The authors stress the need for patient education on the signs of a transfusion reaction, and instructions on what to do if any of these signs are identified. Informed consent is discussed as a necessary requirement before blood is administered. This includes discussion of any alternatives to homologous blood transfusion such as autologous predeposit and intraoperative salvage. Risks of the therapy should also be discussed, and the book outlines the need for documentation that the patient un-

derstands the risks and benefits of the transfusion. A comprehensive list to transfusion reactions is provided.

The mechanics of blood administration are mentioned, but there is no section devoted to the actual phlebotomy, an area which might be considered in future revisions. Components are described in detail, together with their indications and potential complications. The sections on leukocytes transfusion may be of particular interest to the anesthesiologist, especially for ABO and Rh compatibility requirements for this new form of therapy.

The use of plasma products is described, with attention to the national concern expressed about the inappropriate use of fresh frozen plasma as a volume expander. The use of other products that provide this capability with fewer risks is promoted. Specific instructions are provided, with indications for the use of all components involved in the clotting mechanism. The special needs of the hemophiliac and von Willebrands Disease patients are presented.

A whole chapter is directed to the adverse effects of blood transfusion, which offers an excellent guide during those rare occasions when difficulties in the operating room are encountered. This slim volume provides a wealth of information to the practicing anesthesiologist, and is a worthy addition to the library of the practicing anesthesiologist.

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Cardiopulmonary Bypass—Principles and Management

K.M. Taylor, ed. Baltimore: Williams & Wilkins, 1986, 439 pp, \$58.95.

This book with 21 chapters covering a wide variety of aspects of cardiopulmonary bypass is written primarily by British authors and edited by a British cardiothoracic surgeon. Topics range from the history of cardiopulmonary bypass to a chapter on safety during perfusion. In general, the chapters contain abundant references and present current concepts in a straightforward readable way.

Chapter 5 concerns cannulation for cardiopulmonary bypass and nicely covers the "plumbing" aspects of extracorporeal circulation including various incision sites for arterial and venous cannulae and techniques of arterial and venous cannulation. The section on technique for cannulation of the aorta and femoral artery and the complications of cannulation will be very helpful for the neophyte in cardiac anesthesia. The material on cannulation in emergency situations, including cardiac arrest during induction of anesthesia, is likewise very useful. Chapters on oxygenation are very complete and cover practical and theoretical aspects of both bubble and membrane oxygenation. Included in both are pictures of currently available commercial oxygenators. The chapter on blood cell trauma provides a very good discussion of the effects of physical forces on blood cells, including pressure effects, shear stress and wall im-

pact and surface contact and surface tension, as well as a good discussion of the indexes of blood cell trauma.

The material presented on microemboli and micropore filtration is very informative. The discussion of spallation of plastic tubing particles as a source for microemboli is interesting. Photographs showing massive particle entrapment on screen filters during perfusion at activated coagulation time (ACT) less than 300 seconds and accompanying photographs showing minimal particle deposition during perfusion with ACT greater than 400 seconds vividly point out the necessity for maintaining adequate anticoagulation.

The discussions on choice of priming fluids and the pros and cons of pulsatile versus nonpulsatile cardiopulmonary bypass provide much detailed information. Likewise, the material concerning adequacy of perfusion demonstrate the limitations in monitoring adequate perfusion during the routine case. The chapter on safety during bypass nicely outlines the human and nonhuman factors leading to accidents during extracorporeal circulation and includes a complete list of anti-gas embolism devices.

The book does have some obvious drawbacks. References to administering oral diazepam and a cup of tea before general anesthesia are a departure from American practice. The reference to maintaining the rate pressure product below 12,000 during anesthesia for patients with coronary artery disease is outdated. Discussion of administering muscle relaxants as infusions using a nerve stimulator for constant display of myoneutral function is a distracting quirk. The chapter on measurement and monitoring, written by a surgeon, recommends that patients with precarious ventricular function should have noninvasive blood pressure monitoring during induction. Most American cardiac anesthesiologists would probably insert an indwelling arterial line in such patients prior to induction of anesthesia. The list of complications of blood transfusion on page 290 lists many diseases that can be transmitted by blood but fails to mention AIDS. The book contains references to milligrams of heparin rather than the correct terminology, which is units.

Despite these drawbacks, this volume contains a wealth of practical and theoretical information. For the most part it is well written, easily readable, and will be a useful addition to the library of the cardiac anesthesiologist.

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International Anesthesiology Clinics, Anesthesia for Trauma

R.R. Kirby and D.L. Brown. Boston: Little, Brown, 1987, 215 pp, \$24.00.

The Spring 1987 issue of the hard-bound series of International Anesthesiology Clinics is entitled "Anesthesia for Trauma", edited by Robert R. Kirby, MD and David L. Brown,

MD. The familiar green cover contains 11 contributions or chapters, beginning with a spectacular review of the statistical impact of trauma on society, on medicine and, specifically, on the practice of anesthesiology in the United States. This is followed by three chapters on the pathophysiology of shock, crystalloid fluids in resuscitation of shock and blood transfusions, all of which present well-referenced, state-of-the-art information. The chapter on crystalloids contains an annotated bibliography of all important articles relating to the crystalloid versus colloid controversy, which is conveniently arranged by review articles, clinical studies, and animal studies. Although the chapter is moderate and balanced in its presentation of the controversy, it will serve as a valuable resource to those who need to convince colleagues of a particular point of view.

The chapter on transfusions contains *no* information about the AIDS epidemic, which will in the future profoundly influence our practice with regard to blood transfusions in the traumatized patient. In spite of this oversight, I found several pearls of wisdom in its paragraphs. For example, I learned that, "Patients taking beta blocking drugs . . . are more susceptible to hemodynamic deterioration during rapid transfusion secondary to rapidly developing hypocalcemia."

Chapters on choice of anesthetics, ARDS, acute renal failure, and preexisting medical illness are carefully and factually presented, but are heavy reading. In contrast to these, the chapter on infections is written in spirited artistic style, reflecting the personality of the author. Two quotations will demonstrate this point: ". . . a 14 day course of triple antibiotic therapy . . . nearly depletes the diagnostic related group reimbursement for the 'sepsis' diagnosis. . . . Each trauma center and each surgeon has its own tried and true protocol (for prophylactic antibiotics) and attempts to change these protocols often result in emotional displays." The chapter does quite properly deal with the profound impact of infection and sepsis on the delayed morbidity and mortality of trauma.

The final chapters on battlefield anesthesia and wartime trauma are valuable perspectives which remind us that the world is not at peace and information about the anesthetic management of war wounds is not limited to World War II and the Korean and Vietnamese wars but, rather, is being gathered in 1987.

The anesthesiologist who seeks information about the anesthetic management of specific injuries such as head injuries, spine fractures, pneumothorax, burns, etc., will be disappointed, but I guess no one book can cover everything.

I enjoyed reading the book and would recommend it for any physician, student, or nurse interested in improving the care of the traumatized patient.

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Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Cheng TS, ed. The International Textbook of Cardiology. New York: Pergamon Press, 1986, 1297 pp, \$87.50.

Hackel A, ed. Critical Care Transport, Vol. 25, No. 2 of Intl Anesth Clinics. Boston: Little, Brown, 1987, 173 pp, \$20.00 for individual copy or \$53.00 annual subscription for four issues.

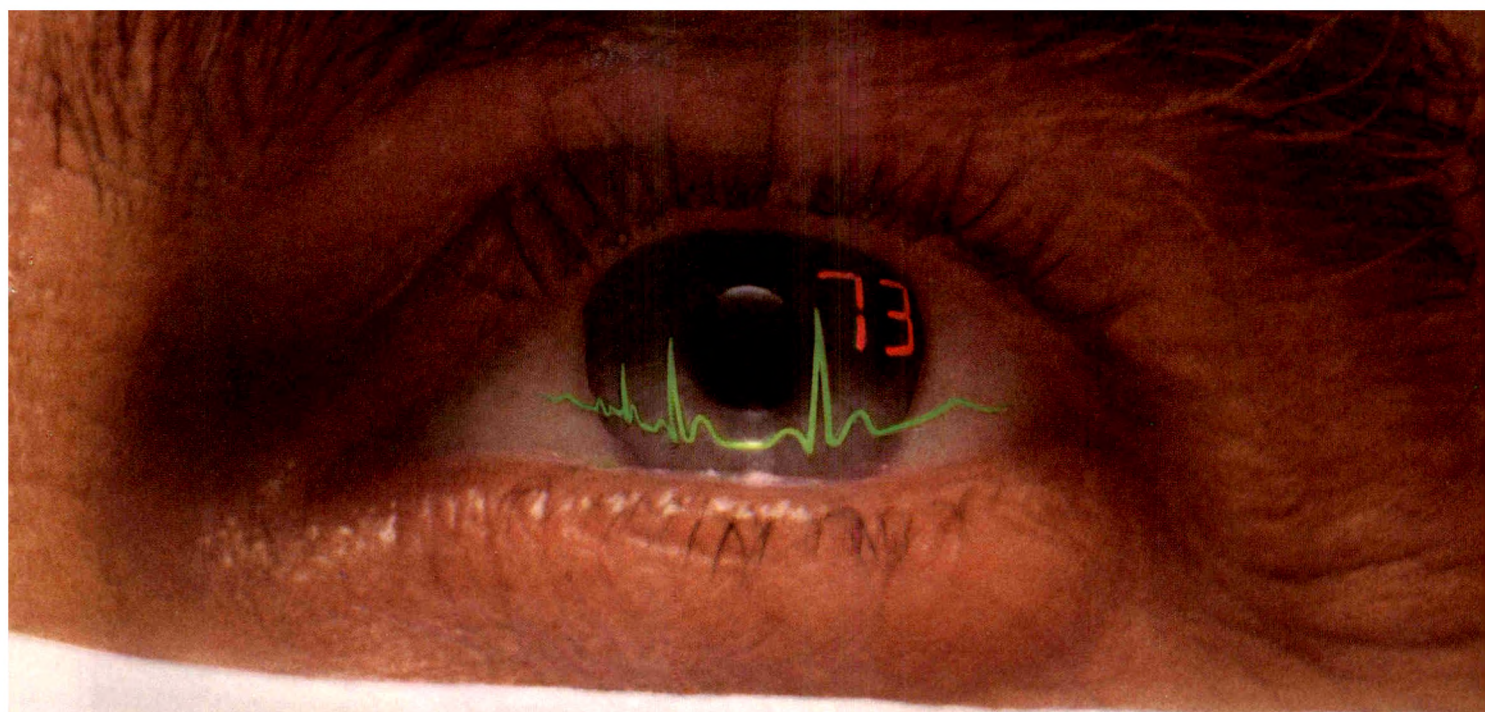
Hinds CJ. Intensive Care, A Concise Textbook. Philadelphia: Bailliere Tindall, 1987, 378 pp.

Farhi LE, Tenney SM, eds. Handbook of Physiology, Section 3: The Respiratory System, Vol. IV, Gas Exchange. Bethesda, MD: Amer Physiol Soc., 1987, 468 pp, \$165.00.

Jenkins LC, Wong DHW. Anesthetic Management of Carotid Endarterectomy. 1987, 179 pp, \$49.95.

Marriott HJL. Rhythm Quizlets, Self Assessment. Philadelphia: Lea & Febiger, 1987, 189 pp, \$16.50.

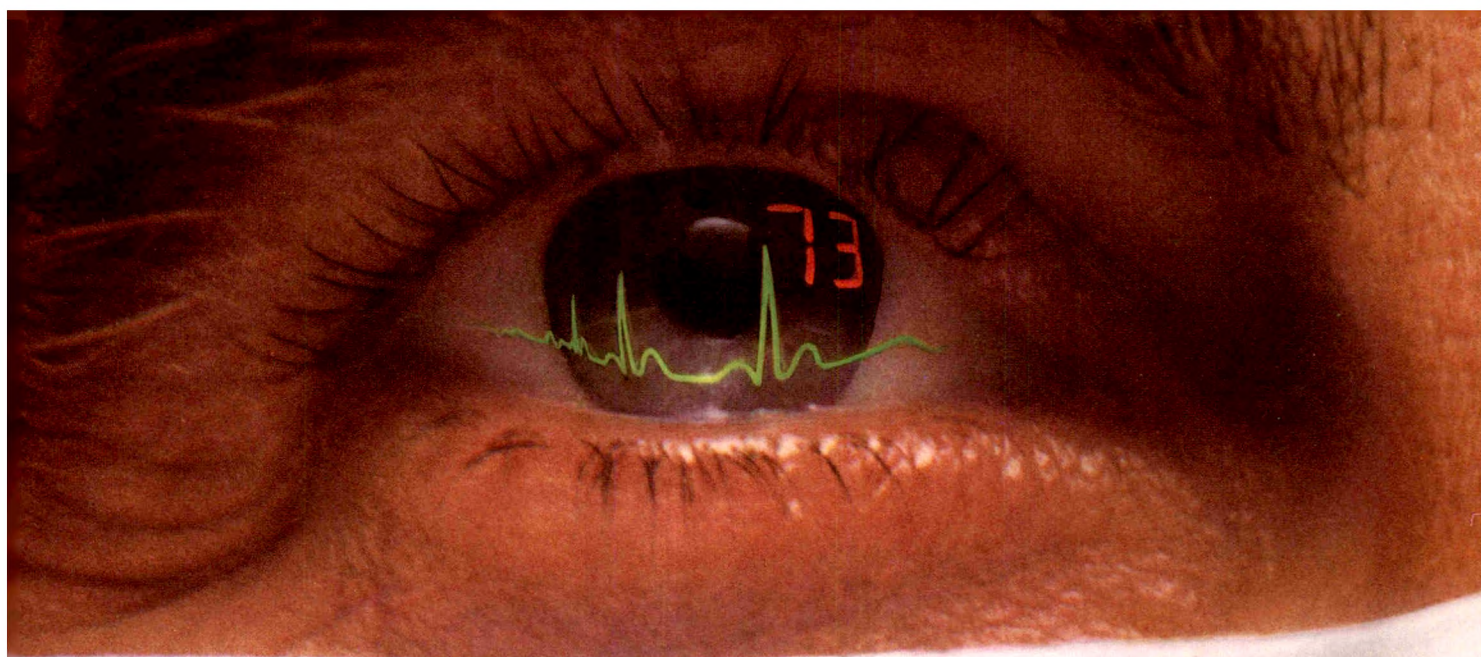
Weintraub H, Levy V-L, eds. Outpatient Anesthesia. Philadelphia: W.B. Saunders, Vol. 5, No. 1, March 1987, 244 pp, \$25.95 for single issue or \$60.00 for four issues.



See for yourself.

**The only surgical muscle relaxant
free of clinically significant
cardiovascular and histamine-
related side effects...**

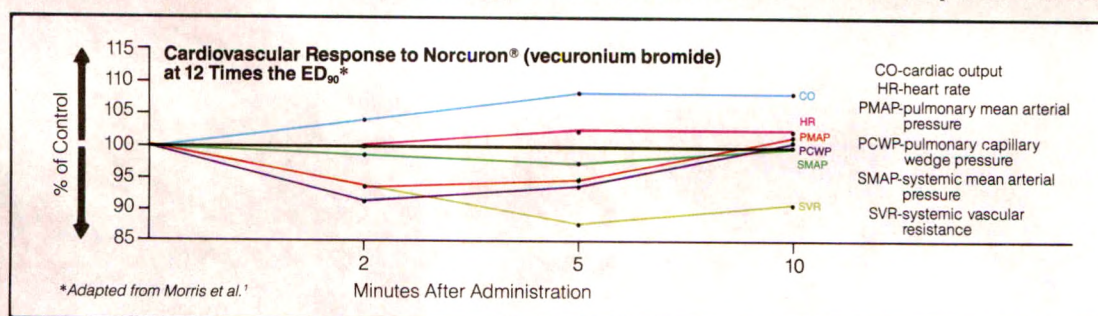
**ideal for your patients, including
those at risk.¹⁻⁵**



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.¹⁻⁴ In fact, even at 12 times effective doses, under halothane anesthesia,¹ NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.

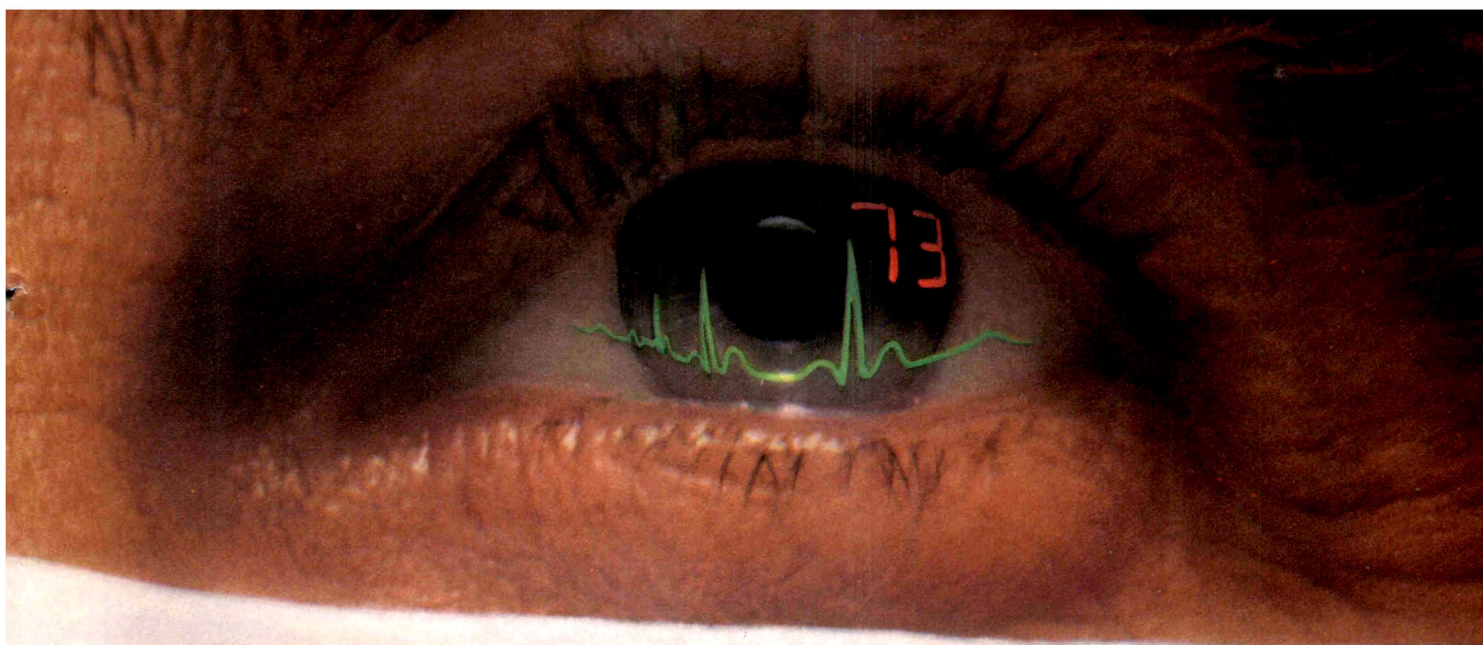


Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED₉₅.⁵

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.⁵

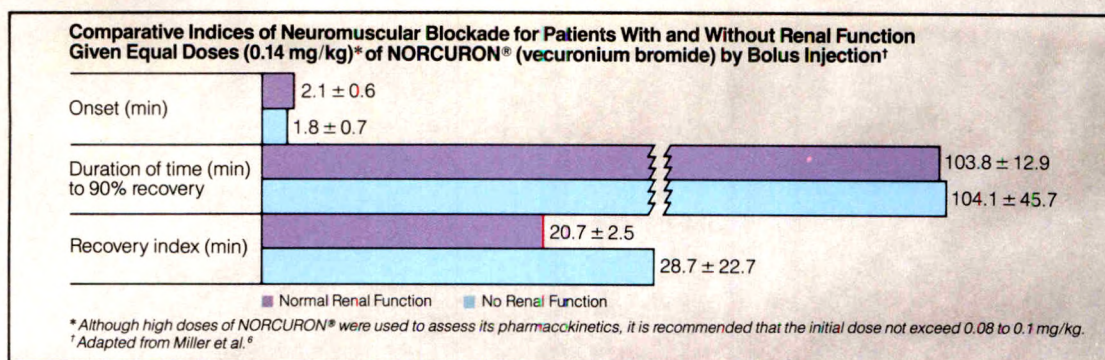
The Effect of Nondepolarizing Muscle Relaxants*				Percent of Control		
Drug	Dose (mg/kg)	xED ₉₅	Histamine	Mean Arterial Pressure	Heart Rate	
Tubocurarine	0.5	1	410	78	116	
Metocurine	0.5†	2	212	79	119	
Atracurium	0.6†	3	192	80	108	
Vecuronium	0.1	1.7	117	100	99	
Vecuronium	0.2	3.5	87	99	102	

*Adapted from Basta et al.⁵
 †0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.⁶

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.⁶



**The surgical muscle relaxant
ideal for virtually all patients
including those at risk.**

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. 2. Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. 3. Krieg N, Crui JF, Booi LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of

vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. 5. Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. 6. Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide)*. Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[2(2,6,6-trimethyl-3,4-dihydro-2H-pyridin-1-yl)propan-1-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED₅₀ (dose required to produce 50% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g., pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/min/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease.) Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose a way and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin), tetracyclines, bacitracin, polymyxin B, colistin, and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. Information on presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve,

low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents,

reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergent intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution

5% glucose in water

5% glucose in saline
Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC #0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC #0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

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Second International

LASER SURGERY CONGRESS

for Otolaryngology—Head and Neck Surgery and Related Specialties

June 22-26, 1988
Opryland Hotel, Nashville, Tennessee

CALL FOR ABSTRACTS

Topics will be: Anesthetic Techniques and Precautions, Bronchoesophagology, Facial Plastic and Reconstructive Surgery—Head and Neck, Instrumentation, Laryngology, Neurotology, Otolaryngology, Pediatric Otolaryngology, Photodynamic Therapy and Research.

Send abstracts (300 words or less) with category to be considered indicated, **by December 1, 1987, to:** Sharon O'Dell, Laser Congress Coordinator, Vanderbilt Division of CME, CCC-5326 MCN, Nashville, TN 37232.

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RAPID ONSET OF ACTION

for prompt control of hemodynamic response
to surgical stimulation*

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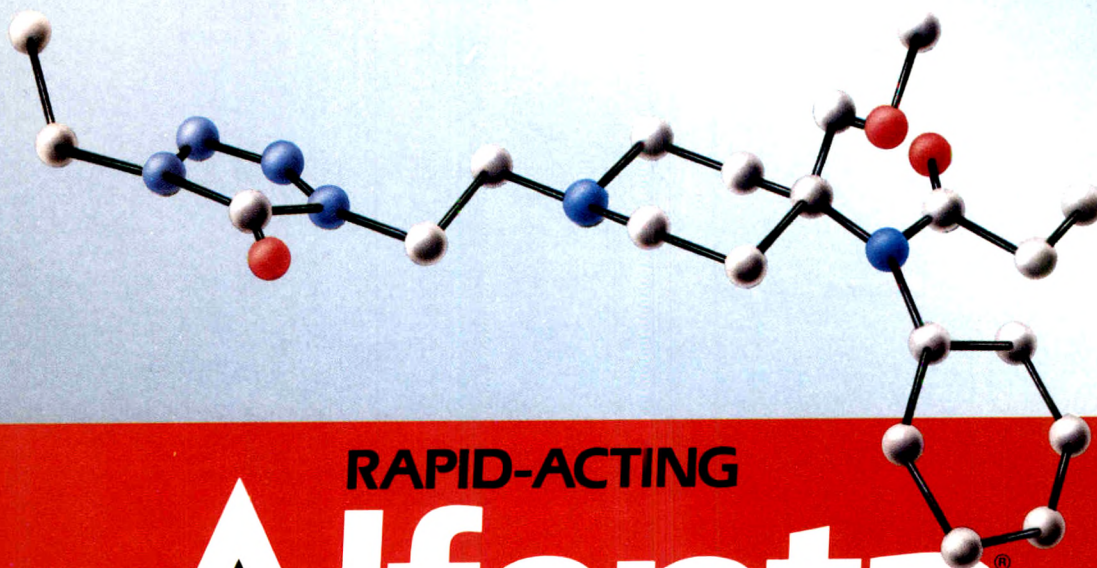
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RAPID-ACTING

Alfenta

(alfentanil HCl) Injection **Ⓢ**

**A PHARMACOKINETIC PROFILE
THAT PERMITS FLEXIBILITY OF
DOSING TECHNIQUE**

**BOLUS/INCREMENTAL
ADMINISTRATION**

for short procedures lasting up to 30 minutes
in spontaneously breathing patients, or for procedures
lasting 30 to 60 minutes in intubated patients

**CONTINUOUS
INFUSION**

for procedures lasting more than 45 minutes
in intubated patients

*As with other opioids, hypotension and bradycardia have been reported.

†As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

See following page for brief summary of Prescribing Information.

RAPID-ACTING

Alfenta®

(alfentanil HCl) Injection

AN OPTIMAL OPIOID ANESTHETIC FOR MOMENT-TO-MOMENT CONTROL

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION, OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg, following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction.

Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO₂. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and non-disturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N=785) %	Fentanyl (N=243) %	Thiopental Sodium (N=66) %	Enflurane (N=55) %	Halothane (N=18) %	Saline Placebo* (N=18) %
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD₅₀ of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSEAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

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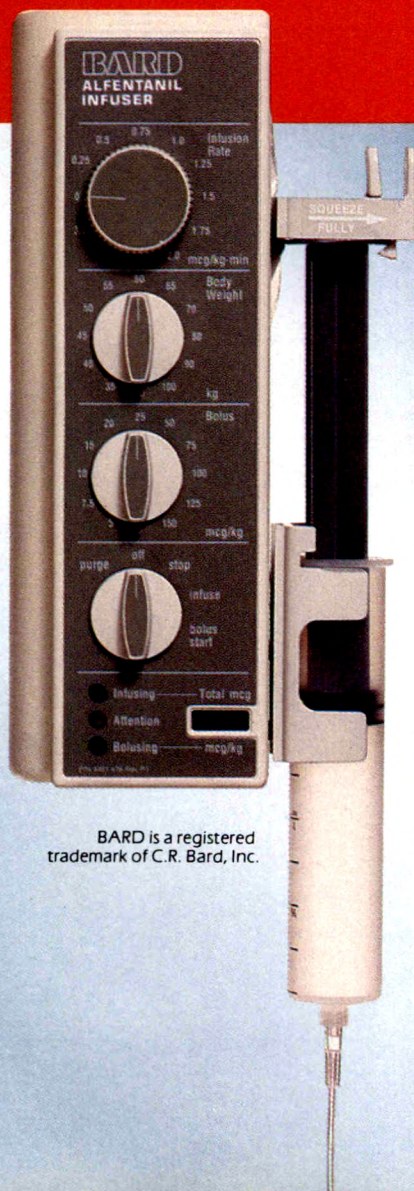
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U.S. Patent No. 4,167,574
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Designed specifically for accurate administration of alfentanil

ELIMINATES TIME-CONSUMING CALCULATIONS

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See preceding page for brief summary of Prescribing Information for ALFENTA® (alfentanil HCl) Injection.

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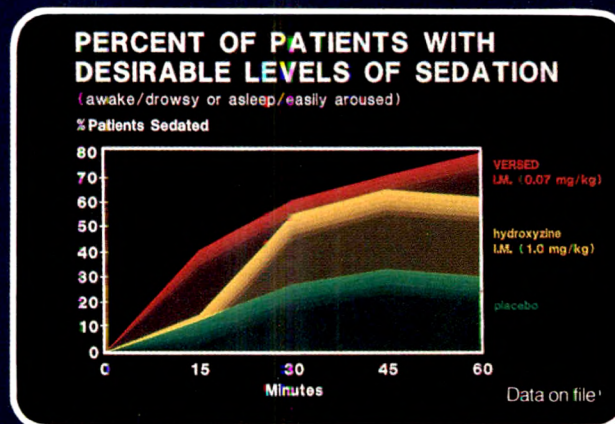
...of hydroxyzine



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Key advantages in premedication

• Sedates faster



Desirable Level of Sedation at 15 minutes	VERSED 43% (64/149)	hydroxyzine 19% (19/101)
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• Virtually painless

Incidence of pain at I.M. injection site²

VERSED	hydroxyzine
alone 4.5% (12/269)	alone 47.1% (64/136)
with other agents 1.8% (2/111)	with other agents 62.7% (32/51)

New

the dilution you've been requesting—

1 mg/mL

for easier titration, easier administration

• Pronounced amnestic effect

The maximum amnestic effect occurred between 30 and 60 minutes after VERSED (0.08 mg/kg) administration.²

Caution patients about driving or operating hazardous machinery after receiving VERSED.



INJECTABLE[®]

VERSED[®]

brand of
midazolam HCl

equivalent to 1 mg/mL and 5 mg/mL

Roche[®] IV

A significant advance in premedication

Please see references and summary of product information on the following page.

References: 1. Data on file (Doc. #069-001), Roche Laboratories. 2. VERSED® (brand of midazolam HCl/Roche) @, Scientific Summary, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, NJ.

**VERSED®
(brand of midazolam HCl/Roche) @
INJECTION**

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: IM: preoperative sedation; to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents; as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen and resuscitative equipment for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation. Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic. Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by about 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia. VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate. 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication. A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

VERSED® (brand of midazolam HCl/Roche)

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred. (See WARNINGS.) In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. (See DOSAGE AND ADMINISTRATION.)

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: **Respiratory:** Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. **Cardiovascular:** Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. **Gastrointestinal:** Acid taste, excessive salivation, retching. **CNS/Neuromuscular:** Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. **Special Sense:** Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. **Integumentary:** Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. **Miscellaneous:** Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients. (See WARNINGS.) **IM use:** Inject deep in large muscle mass. **IV use:** Administer initial dose over 20 to 30 seconds for induction of general anesthesia. For conscious sedation administer initial dose over 2 to 3 minutes. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.



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Classified Advertising

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Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, cooperative, licensed, insured professionals caring about you. Call 1-800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303-598-2788 (CO).

ROCKY MTS./SOUTHWEST

We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, PO Box 5719, Santa Fe, NM 87501. (505) 983-7371.

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:

Individual or small group sessions given in New York City, San Francisco, and Palm Springs. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Call 415-321-1117.

PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS

Send name, address, and phone to Box ANA 5-84-E, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510. Or phone 718-727-9690.

BEST ORAL BOARD PREP

At best price. Includes mental training techniques for Peak Performance. Four practice exams. Reply Best Exam Prep. Anesthesia Department, 5400 Gibson S.E., Albuquerque, NM 87108 (505) 262-7197.

ORAL BOARD REVIEW

Practice exams with critique. Intensive weekend course in Tampa, FL. Next class Dec. 4-6, 1987. Two instructors. Limited class size. Reply: 2656 Gunckel Bl., Toledo, OH 43606, or (419) 729-6325; (419) 475-9641—evenings.

ANESTHESIOLOGIST

Board certified or eligible to join a group of five Anesthesiologist and six Nurse Anesthetists. 350-bed modern hospital in Fredericksburg, Virginia. One hour from Washington, D.C. Reply to Dr. Robert A. Kravetz,

2101 Fall Hill Avenue, Fredericksburg, VA 22401. Or phone (703) 371-2786.

ANESTHESIOLOGISTS & CRNAs

Are you ready for "New Beginnings"? John Paju, CRNA, has been successfully placing his colleagues (both MD and CRNA) into hundreds of temporary and permanent positions throughout the US since 1969. For that personal and helpful touch call John or one of our Placement Coordinators at 1-800-FAST-GAS to discuss exciting job potentials. Send your resume to 619 South State Street, Ukiah, CA 95482. Placements are paid by the employer!

ABA ORAL EXAM REVIEW IN SCOTTSDALE

This weekend course will stimulate, challenge, educate, and prepare candidates for the oral exam, using case discussions. Recent significant research articles will be discussed. Special separate sessions for FMGs with language difficulties. Limited class size. Call for dates and information (602) 264-6340

DIRECTORSHIP

Boarded anesthesiologist needed to head fee-for-service group. East Central Illinois college town. Busy 210-bed hospital with patient draw 100,000. Send CV to Bill Raewolf, SBLHC, Box 372, Mattoon, IL 61938.

SUBSPECIALTY PRACTICE IN PITTSBURGH

The University of Pittsburgh's Eye and Ear Hospital is seeking an anesthesiologist for subspecialty practice in anesthesia for ENT, ophthalmology, plastic/reconstructive, oral/maxillofacial, head and neck, and cranial base tumor surgery. Interest in teaching and research is desirable. Academic appointment at the University of Pittsburgh School of Medicine. Excellent environment and earning opportunity. Please reply with curriculum vitae to: Fred K. Khalouf, DO, Chief, Department of Anesthesiology, Eye and Ear Hospital of Pittsburgh, 230 Lothrop Street, Pittsburgh, PA 15213-2592.

IV DRIP DOSES WHEN YOU NEED THEM!

New pocket chart provides preparation and drip rates for 16 vasoactive and anesthetic drugs in trim, durable format. Send \$5.50 each (5.00 for ten or more) and self-ad-

ressed envelope to Heartcard Productions; 10849 Deborah Drive; Potomac, MD 20854.

VIRGINIA

Anesthesiologist: A six-man group covering two community hospitals in the Tidewater area (between Virginia Beach and Williamsburg) seeking a board-certified or newly trained anesthesiologist. Beautiful and expanding area on the water. Both hospitals have CRNA's. Arthur J. Goldman, MD, Department of Anesthesia, Hampton General Hospital, 3120 Victoria Boulevard, Hampton, VA 23669.

FREELANCE ANESTHETISTS

Temporary and permanent—Medical Anesthesiologists—CRNAs/Home-based throughout the United States. If you need an anesthetist, call (800) 521-6750, ALL-STATES MEDICAL PLACEMENT AGENCY, Box 91, LaSalle, MI 48145, or (313)241-1418 (MI).

MIDWEST WATERFRONT CITY

Fee-for-service group of MDs seeks new partner who is board eligible or certified to practice in 650-bed medical center with minimal obstetrics. Midwest location in progressive waterfront city. Please reply to Box HH31, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum 1/4 page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: **\$1.00 per word, minimum twenty words. Additional fee of \$12.00 for box number ads.** Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be typed double-spaced and mailed in duplicate to:
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PHOENIX, ARIZONA

The University of Arizona Department of Anesthesiology is establishing a new residency training program in Phoenix. Qualified anesthesia faculty are sought both for tenure and clinical tracks at all levels for operating room, ICU, and OB activities in Phoenix. Female and minority applicants are welcome. Contact: Burnell R. Brown Jr., MD, PhD, Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ, 85724. Equal Employment Opportunity/Affirmative Action Employer. Closing date: 12/31/87.

CALIFORNIA

PGY-4 Fellowship position available starting January 1, 1988. HARBOR-UCLA Medical Center is looking for qualified applicants to participate in advanced obstetrical and cardiac anesthesia training. Those interested may contact: Department of Anesthesia, HARBOR-UCLA MEDICAL CENTER, 1000 W. Carson Street, Torrance, CA 90509. An Equal Opportunity Employer

CALIFORNIA: LOS ANGELES COUNTY

Harbor-UCLA Medical Center, Department of Anesthesiology. Unexpected opening in faculty position in the rank of assistant professor. Desires recent graduate of anesthesiology fellowship with research training. Board eligible or certified. Active clinical services, research, and independent residency program in the department. Excellent southern Los Angeles location. Ample academic career opportunities with joint UCLA and Los Angeles County appointments. Competitive compensations. Send statement, C.V., and list of referees to: CHINGMUH LEE, M.D., PROFESSOR AND CHAIRMAN, DEPARTMENT OF ANESTHESIOLOGY, HARBOR-UCLA MEDICAL CENTER, TORRANCE, CA 90509. An Equal opportunity employer.

PEDIATRIC ANESTHESIA

Growing Mid-South Children's Medical Center, affiliated with the University of Tennessee, Memphis, seeks to increase its CRNA staff. The anesthesia care team approach is utilized to provide service for all facets of pediatric anesthesia, including open heart, neuro, and transplantation surgery. Pediatric patient experience preferred. Send CV and references to Director, Pediatric Anesthesia, Le Bonheur Children's Medical Center, One Children's Plaza, Memphis, TN 38103. AA/EEO Employer.

INDIANA

Faculty positions are available at the Assistant and Associate Professor levels. All candidates for these positions must be in the examination system or board certified. Please send a curriculum vitae to Robert K.

Stoelting, M.D., Professor and Chairman, Department of Anesthesia, Fesler Hall Room 204, 1120 South Drive, Indiana University School of Medicine, Indianapolis, IN 46223.

COSTAL CALIFORNIA

Board eligible, University-trained with fellowship and clinical experience, seeking to relocate to coastal California. Enjoys obstetrics and neuro. Proficient with invasive monitoring and epidurals. Excellent letters and C.V. on request. Reply to Box 1140, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

ANESTHESIOLOGIST

BC/BE to join group of 11 MDs with CRNAs in a large hospital located in a pleasant midwestern community on the Great Lakes. Busy practice covering all major surgical subspecialties plus respiratory/ICU involvement and minimal OB. Excellent starting salary and benefits package leading to early partnership. Reply to Box HH35, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

UNIVERSITY OF CALIFORNIA, SAN DIEGO

Department of Anesthesiology is recruiting for six faculty members at the Instructor, Assistant and Associate Professor levels. One tenured position at the Associate Professor level requires demonstrated experience in didactic teaching, clinical training, patient care with an established research interest/experience. The other five positions may or may not be tenured track/tenured. Qualified individuals with specialized clinical skills in cardiac as well as pediatric anesthesia are being sought. Rank and salary commensurate with experience. Must be Board Certified or Board Eligible, and a California medical license is required. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770, UC San Diego, Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California San Diego is an equal opportunity/AA employer. All applications received by December 31, 1987 will receive thorough consideration.

PASS YOUR ORAL BOARDS

Learn how! Reorganize and clarify your knowledge for unique questions and necessary answers. Best preparation by mail for oral format. *Anesthesia Tutorials*; Box 253, 245 East 54 Street, New York, NY 10022.

THE WAUSAU MEDICAL CENTER

A 50-person multispecialty group practice, is seeking a BE/BC individual as the fourth member of our Department of Anesthesiology. Single, 300-bed, modern hospital

located in Wausau. CRNAs also employed by the Medical Center. Full partnership after 2 years. Easy access to lakes, woods, and mountains. Send C.V. to D.K. Aughenbaugh, MD, Medical Director, Wausau Medical Center, 2727 Plaza Drive, Wausau, WI 54401.

CRNAs

Temporary or permanent CRNAs needed in midwestern community. Busy 350+ bed hospital with a patient draw of 200,000. Join established anesthesia practice. Offering competitive salary. Open heart, neuro, some OB and pediatrics. Positions available immediately. Send curriculum vitae to Box 4093, Chesterfield, MO 63006.

ANESTHESIOLOGIST

To join an established private practice. Group of four MDs serving in a small community hospital. 3800 cases per year. Pleasant and right place to raise family. 140 miles from Chicago-Milwaukee. Competitive salary, early partnership. Reply to: P.O. Box 1139, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

DEPARTMENT CHAIRMAN

Louisiana: The Anesthesiology Department of the Louisiana State University Medical Center has an opening for a department chairman with interest in an academic setting. The position's duties include instruction and supervision of residents and students and administration of a large academic department. Qualifications must include graduation from a LCMF accredited medical school, completion of an approved residency training program, eligibility for Louisiana medical licensure, and board certification. Administrative experience or excellent recommendations regarding administrative capabilities are required. The candidate must possess an excellent clinical record and manifest an interest in academics and research. Specialty training or experience is desired. The salary and level of faculty appointment will be commensurate with qualifications. Inquiries should be directed immediately along with a current Curriculum Vitae to: Fred J. Stucker Jr., MD, Chairman of the Search Committee, Louisiana State University Medical Center in Shreveport, PO Box 33932, Shreveport, LA 71130-3932. Affirmative Action/Equal Opportunity Employer.

RESPIRATORY THERAPY SECTION CHIEF

Board Eligible or board certified anesthesiologist wanted to be Section Chief of Respiratory Therapy Department. Duties limited to above. Formal training required. Please reply to Box HH33, c/o *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

ANESTHESIOLOGIST

BC or BE for immediate opening in beautiful lakeside community 1 hour northeast of Detroit. Five person group servicing two hospitals needs sixth anesthesiologist to supervise CRNAs and to administer some anesthesia. Excellent wage & benefit package. Early Partnership. Please send C.V. to Eric Robb, MD or Ann Marie Ernst, DO, Anesthesia Associates of Port Huron, P.C., 929 Division St., PO Box 611368, Port Huron, MI 48061-611368.

TENNESSEE ANESTHESIOLOGIST

Directing Anesthesia services of large Regional Medical Center including Labor and Delivery, Trauma Center, Ambulatory, and Operating Rooms. Full-time faculty position in University with emphasis on teaching, patient care, and research. Faculty position: Assistant Professor-Associate Professor, salary commensurate. Must be diplomate of ABA. Must meet Tennessee license requirements. Interest and experience in teaching, patient care, and management preferred. Excellent opportunity for private practice with teaching and research activities. Send CV, bibliography, and three references to: John J. Angel, MD, Chairman, University of Tennessee, Memphis, Department of Anesthesiology, 800 Madison Avenue, Memphis, TN 38163. AA/EEO Employer.

TENNESSEE

Pediatric Anesthesiology—Full-time position at level of Instructor/Associate Professor with emphasis on teaching, patient care, and clinical research. Assigned to large Children's Medical Center. Must meet Tennessee license requirements and ABA diplomat or eligible for ABA exam. Send C.V., bibliography, and three references to: John J. Angel, MD, Chairman, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, FG17, Memphis, TN 38138. AA/EEO Employer.

CHIEF ANESTHESIOLOGIST, MARYLAND

and two staff anesthesiologists needed to form anesthesiology department of large multispecialty group providing care for Blue Cross/Blue Shield affiliated HMO as well as large FFS practice. Department will administer anesthesia to patients in local acute care hospital as well as in outpatient surgical suite. Excellent salary and benefit package. Fully paid 5/7 malpractice insurance. Excellent support services and modern facilities. Located between Baltimore and Washington in Columbia, Maryland. Abundant cultural, recreational, and academic advantages. Possibility of teaching appointment at prestigious local medical school. Please direct inquiries to: Patuxent Medical Group, Columbia Free State Health Systems, Two Knoll North Drive, Columbia, MD 21045. Attention: Beth Talbot-Sanders.

ANESTHESIOLOGIST

Large Chicago area hospital with a residency program seeks a qualified attending anesthesiologist with strong interest in teaching and research. Very competitive salary and fringe benefits, commensurate with experience. Board certification and 4 years' training preferred. Please send curriculum vitae to Box HH34 c/o *Anesthesia and Analgesia*, 333 Cedar Street, New Haven CT 06510.

AAA ANESTHESIOLOGIST

To confidentially explore salaried and contract positions available at our facilities in the U.S., reply with CV and include availability date, licensure status, and geographical preference. NAMA Professional Bldg., Suite 200, 138 East Street, Carlisle, MA 01741.

SOUTHERN CALIFORNIA

The Beaver Medical Clinic, Inc., A 34-physician multispecialty group practice located in Southern California is currently recruiting a well-trained anesthesiologist to join its Anesthesiology Department. Group's anesthesia work in call schedule of 7-man anesthesia staff in support of the 200-bed Community Hospital and free-standing Surgery Center. Liberal guaranteed starting salary with productivity bonus compensation package, malpractice paid. Excellent fringe benefit package and potential shareholder status within 2 years. Practice located in family oriented community with ideal opportunity for year round outdoor activities. Send CVs to: Beaver Medical Clinic, Inc., ATTN: Melanie Vale, 2 West Fern Avenue, Redlands, CA 92373.

MIDWEST: CHIEF OF ANESTHESIA

Chief of Anesthesia to head department and staff anesthesiologists needed in midwestern city of approximately 150,000. Busy 300+ bed hospital. Expanding practice, open-heart, little OB and pediatrics. Chief must be board certified with administrative experience and staff must be board certified or eligible. Fee-for-service practice. Well equipped department. Positions available immediately. Send curriculum vitae to Box 4093, Chesterfield, MO 63006.

CLINICAL DIRECTOR OF ANESTHESIOLOGY

Anesthesiologist: Unusual opportunity for mature Board Certified MD who is interested in an intellectually stimulating, yet physically nondemanding position as Clinical Director of Anesthesiology. No scheduled cases, no call, no rounds. Good to excellent financial package with the security of a multi-institution-based company. Please include Curriculum Vitae, three references, and salary expectations with first reply. Box HH37, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

MARYLAND

Anesthesiologist BC/BE sought for three-member group serving modern 200-bed community hospital. Six CRNAs. 4,000 cases/year. All surgical subspecialties except cardiac. Regional trauma center. Moderate OB. Active new outpatient surgery unit within hospital. Community of 25,000 in mountains of Western Maryland. Close to four-season recreational opportunities. Position available January 1988, but will wait for right person. Salary first, leading to partnership. Send CV and references to: W.R. Hodges III, MD, Department of Anesthesia, Memorial Hospital and Medical Center, Cumberland, MD 21502.

BOARD-CERTIFIED ANESTHESIOLOGIST

Northeastern Ohio teaching hospital with an approved, 4-year residency program in anesthesiology seeks a board-certified anesthesiologist with extensive interest and experience in research and teaching. Responsibilities will include clinical practice, house staff education, and clinical investigation. Excellent salary and benefits leading to early partnership. Send curriculum vitae and references to: John G. Poulos, M.D., Chairman, Department of Anesthesiology, Huron Hospital, 13951 Terrace Road, Cleveland, OH 44112.

UTAH

The University of Utah seeks Anesthesiologists who are Board Certified for positions at Instructor to Associate Professor levels. Candidates should have expertise in cardiac, pediatric or obstetrical anesthesia with experience in clinical or basic science research. Position commensurate with experience. Send curriculum vitae to: K.C. Wong, M.D., Chairman, Department of Anesthesiology, University of Utah Health Science Center, 50 North Medical Drive, Salt Lake City, Utah 84132. Equal Opportunity/Affirmative Action Employer. Closing date: November 30, 1987, or until qualified candidate identified.

VAIL, COLORADO

Immediate opening for anesthesiologist in beautiful Vail, Colorado. Vail Valley Medical Center is a community hospital serving the greater Vail area. No neuro or cardiac. This is an excellent fee-for-service position in a mountain community with superb recreational opportunities. Send all inquiries, with resume, to: Ray McMahan, 181 West Meadow Drive, Vail, CO 81657.

ANESTHESIOLOGIST—BE

to join one MDA and three CRNAs at 100-bed hospital in intermountain west. Two weeks on and two weeks off. Nearby hunting, fishing, skiing, and boating. Reply to Box II38, % *Anesthesia & Analgesia*, 333 Cedar Street, New Haven, CT 06510.

ANESTHESIA RESEARCH

The Department of Anesthesiology at Loyola University Stritch School of Medicine, Maywood, Illinois, located in the western suburbs 10 miles from downtown Chicago, is recruiting one faculty member with established research experience and/or a strong desire to pursue research in Anesthesia. Excellent laboratory support is in existence. Minimum requirements are Board Certification in Anesthesiology with experience in teaching, research, and clinical training, and Illinois state licensure or eligibility. Appointment will be at the level of Associate Professor or Professor. Salary commensurate with qualifications and experience. Please send letter, curriculum vitae, and names/addresses of three references to: T.L.K. Rao, MD, Chairman, Department of Anesthesiology, Loyola University Stritch School of Medicine, 2160 South First Avenue, Maywood, IL 60153. Loyola Medical Center is an equal opportunity employer.

SALT LAKE CITY

VAMC Immediate opening available for full-time anesthesiologists. This service is part of the residency training program at the University of Utah. Experience in cardiothoracic anesthesia is desirable (BE/BC). Ideal mixture of clinical practice, teaching, and research opportunities with university appointment. Local activities include skiing, fishing, camping, and hunting within 30 minutes of downtown. The area also offers the arts, professional sports, and many local points of interest. Send curriculum vitae and letters of reference to G. Richard Lee, MD, Chief of Staff, V.A. Medical Center, 500 Foothill Blvd., Salt Lake City, Utah 84148 or call (801) 582-1565, Extension 1505.

LOUISIANA

ANESTHESIOLOGIST, Board Certified or Eligible. Pediatric CV Anesthesia and Pain

Clinic experience required. Group Practice—Progressive Community Medical Center, suburb of New Orleans. CV to Director, Anesthesia Associates, PO Box 1400, Marrero, LA 70073-1400.

IOWA: NEUROANESTHESIA FELLOWSHIPS

The Neuroanesthesia Group at the University of Iowa Hospitals and Clinics is taking applications for 1988–89. The group provides >1500 neurosurgical anesthetics/yr, and three funded laboratories. OR projects concerning hemodynamics, electrophysiology, and pharmacology are underway, while laboratory efforts are ongoing in the cerebrovascular and metabolic physiology anesthetics and ischemia/trauma, and in neuromuscular pharmacology. Methods available include neurohistology, autoradiography (CBF and CMRG), H2 clearance (CBF), processed EEG and EP, microgravimetry, voltage clamping. Fellows are expected to participate in clinical and/or laboratory research, and should have completed at least 24 months of approved Anesthesia residency training. Contact Michael M. Todd, MD, or David S. Warner, MD, Neuroanesthesia Research Group, Department of Anesthesia, University of Iowa Hospitals and Clinics, GH6SE, Iowa City, IA 52242.

ILLINOIS

Academic department seeking additional faculty at level of Assistant or Associate Professor. Candidates should be qualified in clinical care, teaching, and research. Minimum requirement is a 4-year educational continuum or its equivalent. Faculty rank and salary commensurate with training and experience. Send Curriculum Vitae to: T.L.K. Rao, MD, Chairman, Department of Anesthesiology, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60513.

FELLOWSHIP/CRITICAL CARE MEDICINE

One year fellowships in Critical Care Medicine, beginning July 1, 1988, are available at the Maryland Institute for Emergency Medical Services Systems. The Institute specializes in the care of adult trauma victims, and is the center of a state-wide trauma network. Approximately 45 beds (of a total of 96) are devoted to intensive care. Admission numbers are about 2800/year. Opportunities for elective experience in Pediatric ICU, trauma anesthesia, open heart recovery, and hyperbaric medicine are available. Respond to: John S. Britten, M.D., Department of Critical Care Medicine, c/o MIEMSS, 22 S. Greene Street, Baltimore, MD 21201.

WANTED: THREE ACADEMIC ANESTHESIOLOGISTS

at the Instructor or Assistant Professor level with particular interest in clinical anesthesia, subspecialty areas, and/or research. Must have completed a 4-year residency in anesthesiology, and be Board Certified or Board Eligible. One position has an anticipated starting of January 2, 1988 or later, and two have an anticipated starting date of July 1, 1988 or later. Stipend negotiable and dependent on credentials. Interested parties should forward letter including Board status, curriculum vitae, and bibliography to: Robert Redfern, M.D., Search Committee Chairman, Department of Anesthesiology, University Hospital of Jacksonville, 655 West 8th Street, Jacksonville, FL 32209. Application deadline is December 4, 1987. Equal Employment Opportunity/Affirmative Action Employer.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1988 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to \$25,000 are invited for the 1988 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **December 8, 1987**.
- The official application for the Award must be used. This form, and the guidelines for applicants, are available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1988 Award(s) will be announced at the Annual Scientific Meeting (62nd Congress) of the International Anesthesia Research Society to be held at the Hotel Inter-Continental, San Diego, California, March 5-9, 1988.

Anesthesia Foundation Book Award

The Anesthesia Foundation announces the fifth award of five thousand dollars for a book judged to be the best written in the field of anesthesiology and submitted before September 15, 1988. The award will be given only to an anesthesiologist working and living in North America.

The award will be given only for a first edition. A book may not have more than two authors, and the senior author must be an anesthesiologist. Books that are part of a series, where each chapter has a different author, will not be eligible. Symposia and reports of meetings are also ineligible. Textbooks will be considered if there are not more than two authors.

The award will be based on timeliness, timelessness, originality, teaching value, sophistication, literary style, illustrations, scientific excellence, succinctness, impact, permanent value, format, and references.

If, in the opinion of the judges, no book merits the award, no award will be made.

Books may be submitted by the author or the book publisher. Books must be received no later than September 15, 1988. Books may have a copyright date of 1987 or 1988, but if they are received after September 15, 1988, they will be considered for the following award, provided a sixth book award is offered.

One copy should be sent to each of the three judges:

Nicholas M. Greene, MD, Professor
Department of Anesthesiology
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

Joseph F. Artusio Jr, MD
Secretary, The Anesthesia Foundation
525 East 68th Street
New York, New York 10021
Attention: Department of Anesthesiology

Leroy D. Vandam, MD
Department of Anesthesia
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115

CALIFORNIA: UCLA Department of Anesthesiology and Olive View Medical Center are seeking a faculty person to serve as Chief of the Anesthesiology Service at Los Angeles County-Olive View Medical Center, one of the primary UCLA affiliated teaching hospitals. Olive View is a new 350-bed state-of-the-art hospital, which has completely replaced an older facility. This opening represents an exceptional opportunity to develop a university affiliated service in an entirely new hospital. Salary is commensurate with the position and academic qualifications. Candidates must be eligible for a California state license and provide proof of employment eligibility. Equal opportunity employer. Address correspondence with references and curriculum vitae to: **STUART F. SULLIVAN, M.D., CHAIRMAN, SEARCH COMMITTEE FOR CHIEF OF ANESTHESIOLOGY SERVICE AT OLIVE VIEW MEDICAL CENTER, DEPARTMENT OF ANESTHESIOLOGY-BH-533-CHS, UCLA SCHOOL OF MEDICINE, LOS ANGELES, CA 90024-1778.**

Also openings for Physician Specialist, Anesthesiology available. Respond to: **BRUCE PICKEN, M.D., MEDICAL DIRECTOR, OLIVE VIEW MEDICAL CENTER, 14445 OLIVE VIEW DRIVE, SYLMAR, CA 91342 (818) 364-4380.**

MOVING?

To avoid interruption in your receipt of this Journal, we need to know your new address—six weeks in advance.

When writing us, be sure to type or print clearly your name and your new address—complete with zip code. It is essential that you also list your old address.

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Regonol (pyridostigmine bromide injection USP)

BRIEF SUMMARY—(Please consult full package insert, enclosed in every package, before using Regonol)

INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties: muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg/kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

HOW SUPPLIED—Regonol is available in:

5 mg./ml.: 2 ml. ampuls—boxes of 25—NDC-0052-0460-02
5 ml. vials—boxes of 25—NDC-0052-0460-05

REFERENCES:

1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975.
2. Ravin MB: Pyridostigmine as an antagonist of d-tubocurarine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.



Organon Pharmaceuticals
A Division of Organon Inc.
West Orange, N.J. 07052

OR-5091

In

Reversal

of nondepolarizing
muscle relaxants,
don't look for what's better...
...look for what's best

Regonol®



(pyridostigmine
bromide injection, USP)
when compared to neostigmine

- ☐ Clinically fewer side effects
- ☐ Significantly lower degree and incidence of:
 - 1) Bradycardia
 - 2) Salivation
 - 3) Gastrointestinal stimulation
- ☐ Wide margin of safety^{1,2}



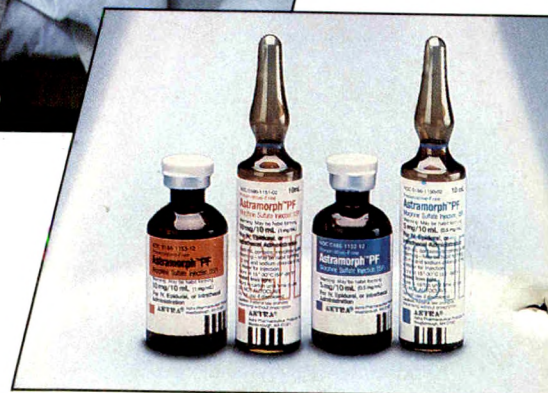
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INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents, intestinal and urinary obstructions of mechanical type

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and anti-shock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg/kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

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1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975.
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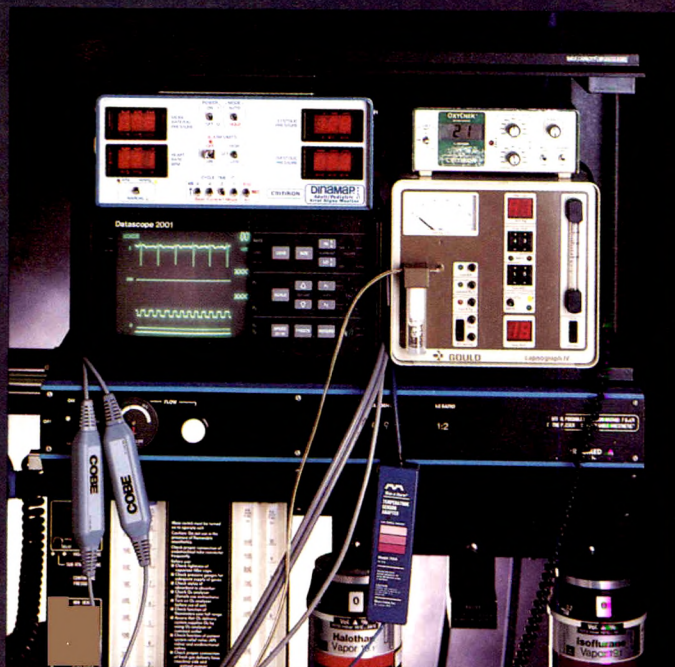
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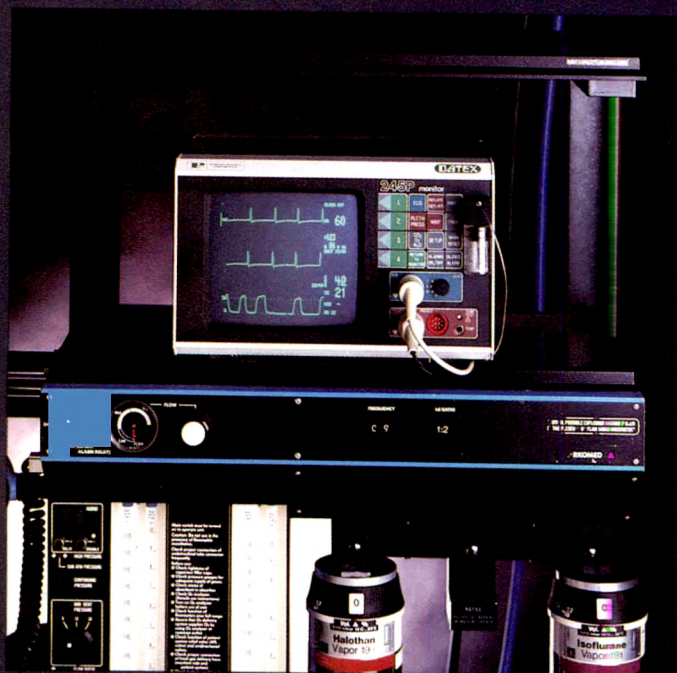
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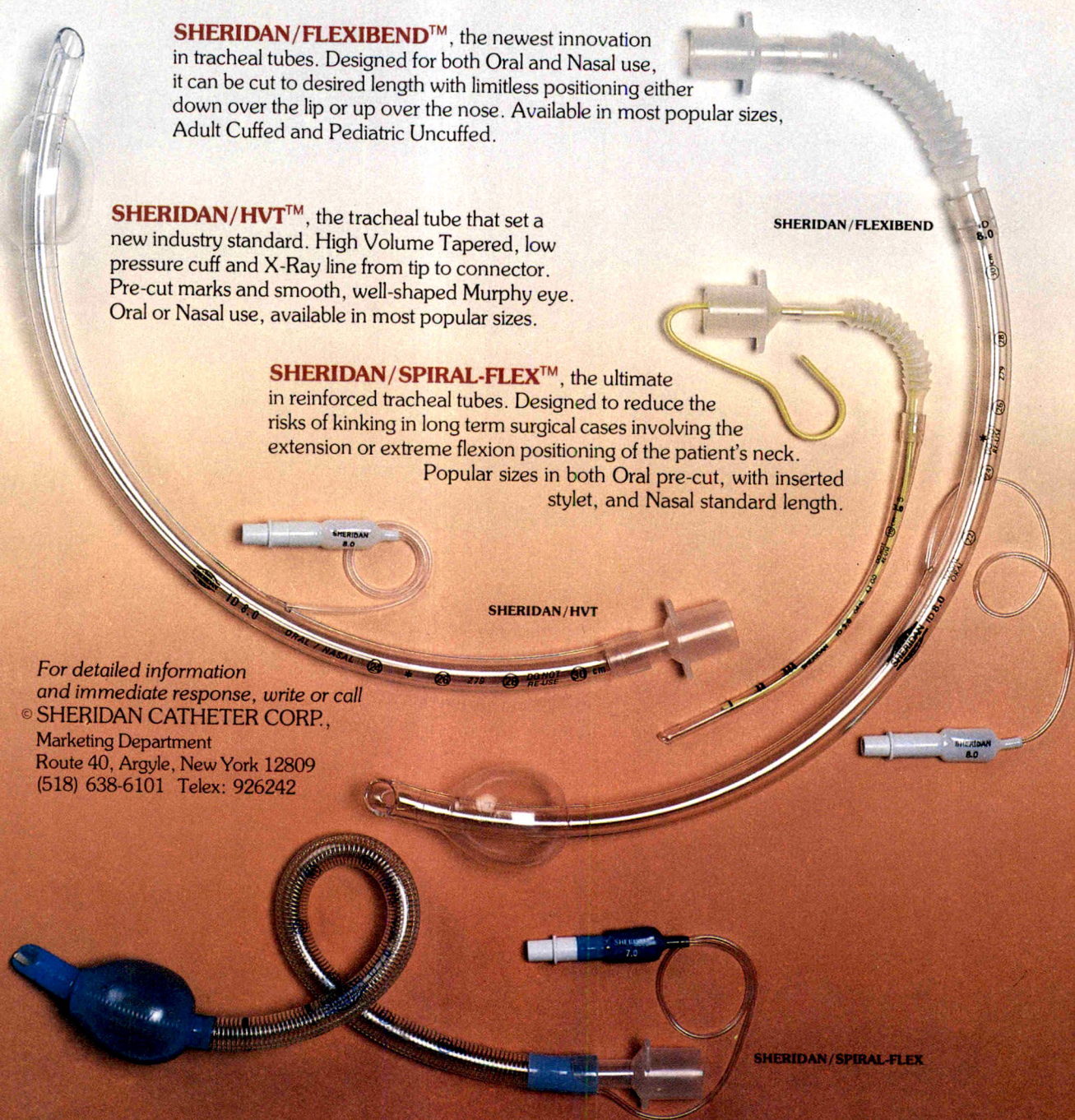
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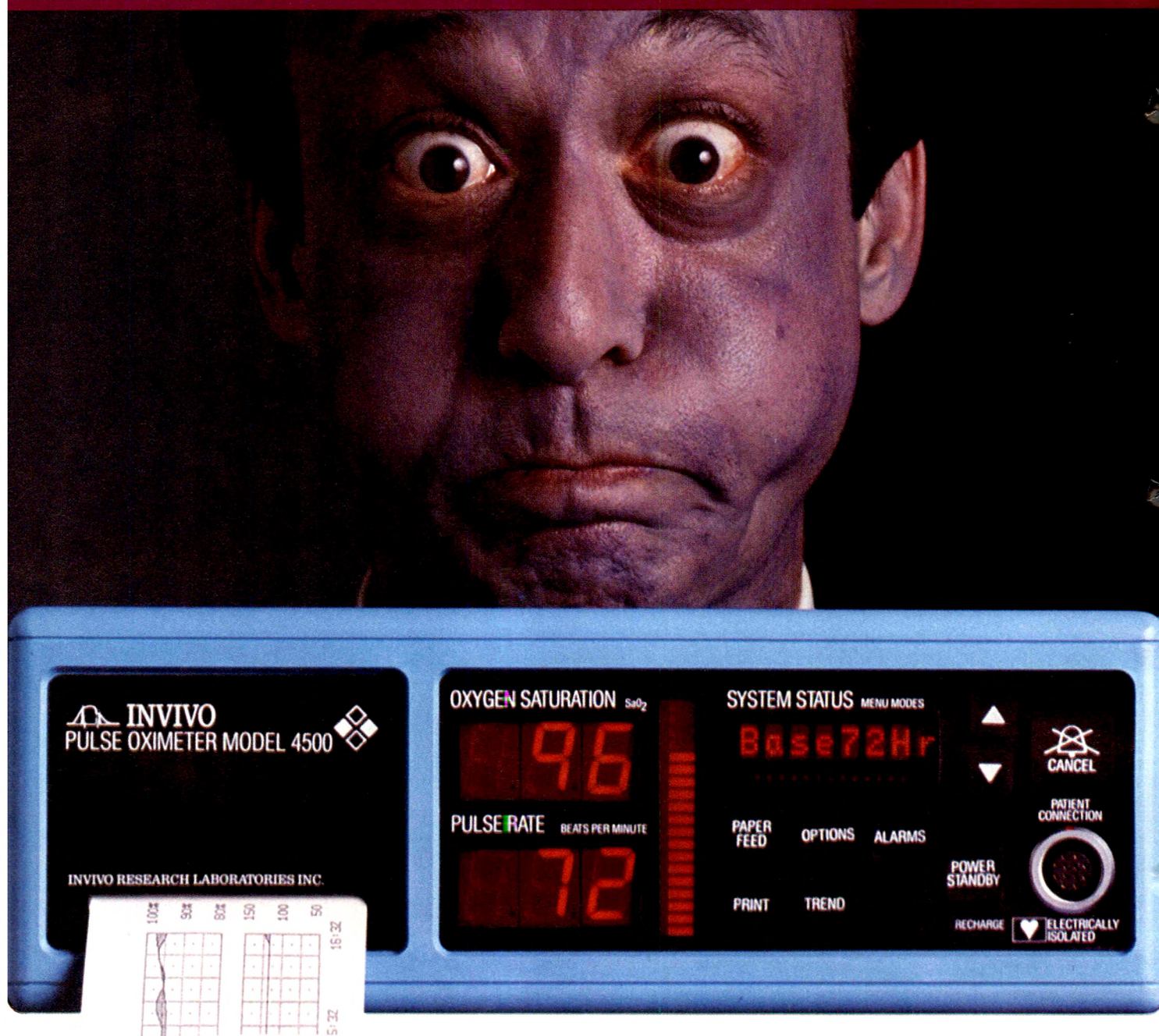
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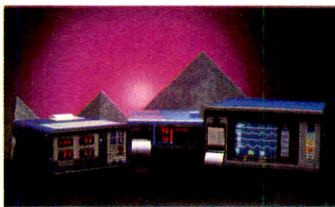


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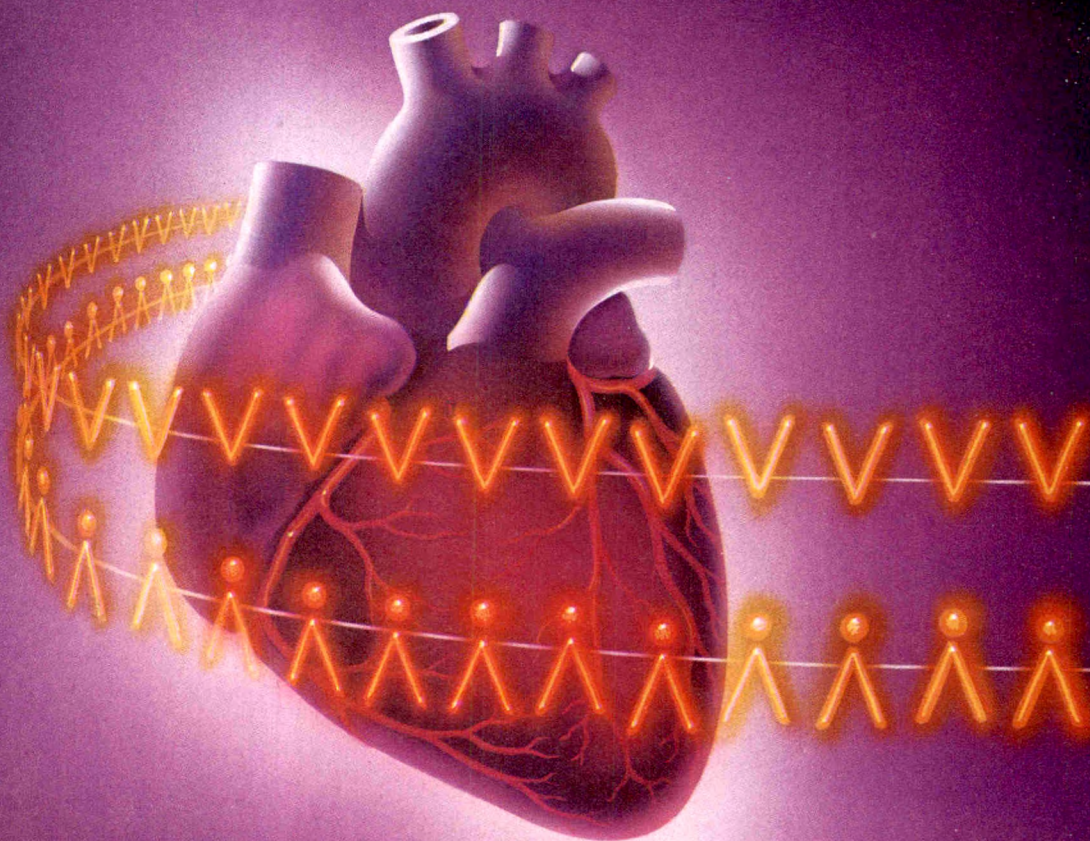
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WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to $1/4$ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 $\mu\text{g}/\text{kg}$, 2) administration of a full paralyzing dose of a neuromuscular blocking agent

following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 $\mu\text{g}/\text{kg}$) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 $\mu\text{g}/\text{kg}$). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion

**THE PRIMARY ANESTHETIC
THAT KEEPS PATIENTS
ON TRACK**

SUFENTA[®] **(sufentanil citrate) Injection**

Predictable control for longer, more stressful procedures

PROVIDES smooth induction¹

**BLUNTS hemodynamic response to intubation
and surgical stimulation²**

**REDUCES need for vasoactive drugs in
the intraoperative and postoperative periods¹**

**RESULTS in lower postoperative morbidity after
aortic surgery compared with isoflurane³**
(in a randomized study comparing sufentanil and isoflurane)

CONVENIENT: Fewer ampoules to open

of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD₅₀ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm

Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD₅₀ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD₅₀s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSEAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).



**JANSSEN
PHARMACEUTICA**

Janssen Pharmaceutica Inc.
Piscataway, NJ 08854

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U.S. Patent No. 3,998,834
7618504-M

January 1986, March 1986

JPI-710

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

62nd CONGRESS - March 5-9, 1988

Marriott-San Diego

(formerly Hotel Inter-Continental, San Diego, California)

PRELIMINARY MEETING INFORMATION

PROGRAM / REGISTRATION / HOTEL INFORMATION: Will be mailed mid-December to all IARS members. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members should request information from the Cleveland Office: 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephone: (216) 295-1124.

MEETING SCHEDULE: Registration: Saturday, March 4, 1-6 pm

Scientific Program: Sunday, March 5 through Wednesday, March 9

Exhibits: Sunday, March 5 through Tuesday, March 8

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture:

"Anesthesia, Science and Art"

Frank M. Standaert, MD, Dean of the Medical Faculty,
Medical College of Ohio at Toledo

REVIEW COURSE LECTURES:

J. Jeffrey Andrews, MD
Jeffrey L. Apfelbaum, MD
Paul G. Barash, MD
Jonathan L. Benumof, MD
D. Ryan Cook, MD
Benjamin G. Covino, MD
Judith H. Donegan, MD
Edmond I. Eger II, MD
John H. Eichhorn, MD

Mieczyslaw Finster, MD
Paul R. Hickey, MD
John T. Martin, MD
Charles H. McLeskey, MD
Joseph M. Messick Jr, MD
Ronald D. Miller, MD
Richard L. McCammon, MD
Terence M. Murphy, MD

Walter S. Nimmo, MD
Richard J. Palahniuk, MD
J. Gerald Reves, MD
Myer H. Rosenthal, MD
John J. Savarese, MD
Linda C. Stehling, MD
John H. Tinker, MD
Kevin K. Tremper, MD
Paul F. White, MD

PANEL: *New Perspectives in Pediatric Anesthesia*

Barbara W. Brandom, MD
Lynn M. Broadman, MD
D. Ryan Cook, MD
Paul R. Hickey, MD

PANEL: *Perioperative Blood Transfusion*

Gene Berkman, MD
Norig Ellison, MD
Ronald D. Miller, MD
Linda G. Stehling, MD
Leslie E. Silberstein, MD

*153 Scientific Papers . . . 114 Scientific Posters . . . Theme Luncheons
Scientific Exhibits - Technical Exhibits - Product Seminars*

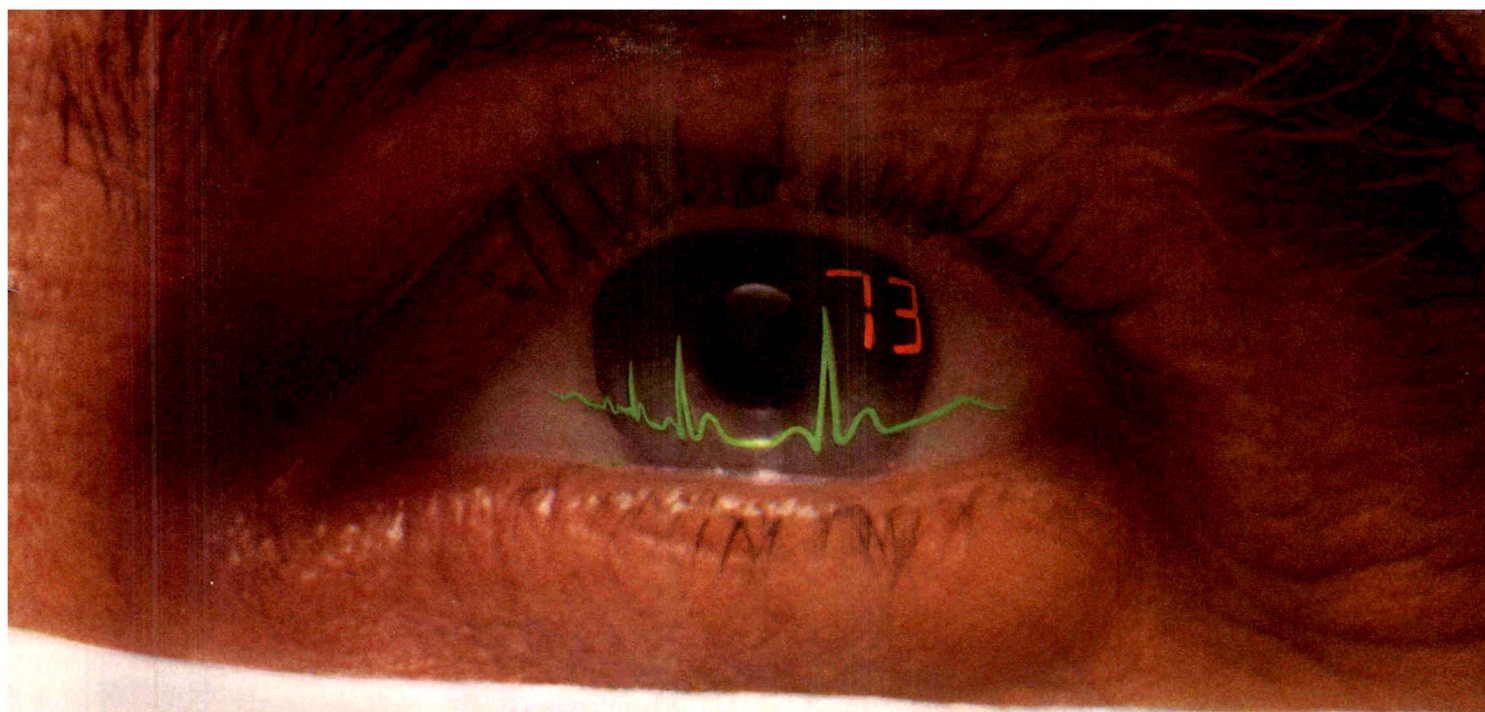
REGISTRATION • CME CREDIT • AIR TRAVEL • HOTEL

FEES: IARS Members	\$175 (\$200 on-site)
IARS Educational Members	No Fee
Nonmembers	\$350 (\$400 on-site)
Nonmember Residents	\$50 (with certification)

CME CREDIT: ACCME/AMA: Category 1: 31 hours

SPECIAL AIR FARES: Both Delta Airlines and United Airlines, in cooperation with the IARS, will provide reduced fares for round-trip travel to San Diego. Full details will be included in the preliminary program mailing, or can be obtained by calling the following numbers and referring to IARS meeting and file/account numbers shown:
United: 1-800-521-4041—Account No. 8063-H; *Delta:* 1-800-241-6760—File No. P-0095

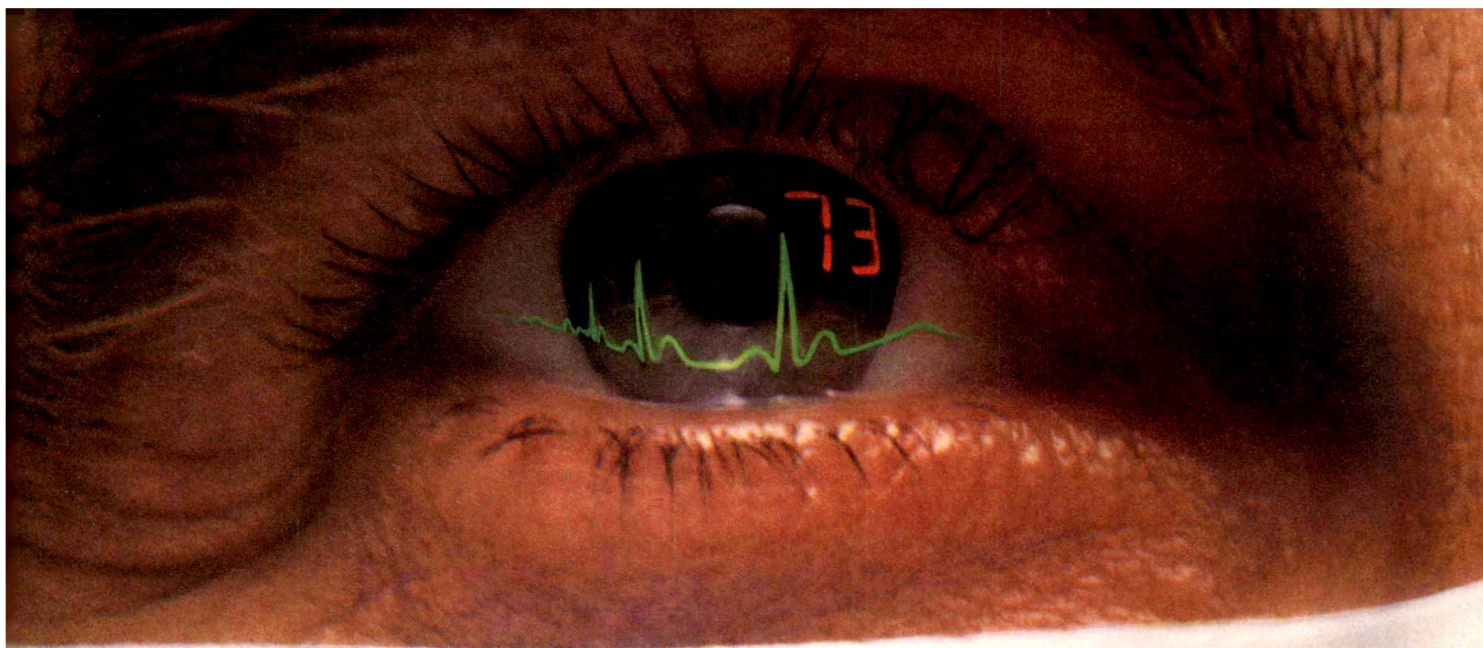
HOTELS: The headquarters hotel where all meetings and exhibits will be held is the Marriott-San Diego (formerly the Inter-Continental), 333 West Harbor Drive, San Diego, CA 92101. A limited number of rooms will also be available at the Omni Hotel. Reservations must be made on IARS meeting hotel reservation form.



See for yourself.

**The only surgical muscle relaxant
free of clinically significant
cardiovascular and histamine-
related side effects...**

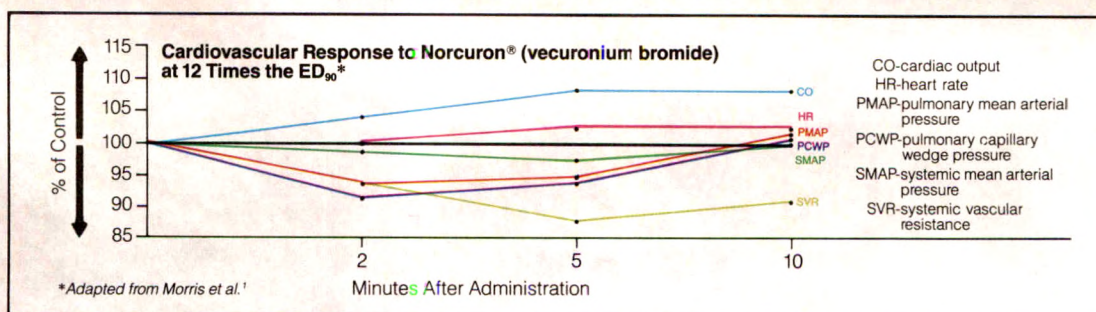
**ideal for your patients, including
those at risk.¹⁻⁵**



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.¹⁻⁴ In fact, even at 12 times effective doses, under halothane anesthesia,¹ NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.

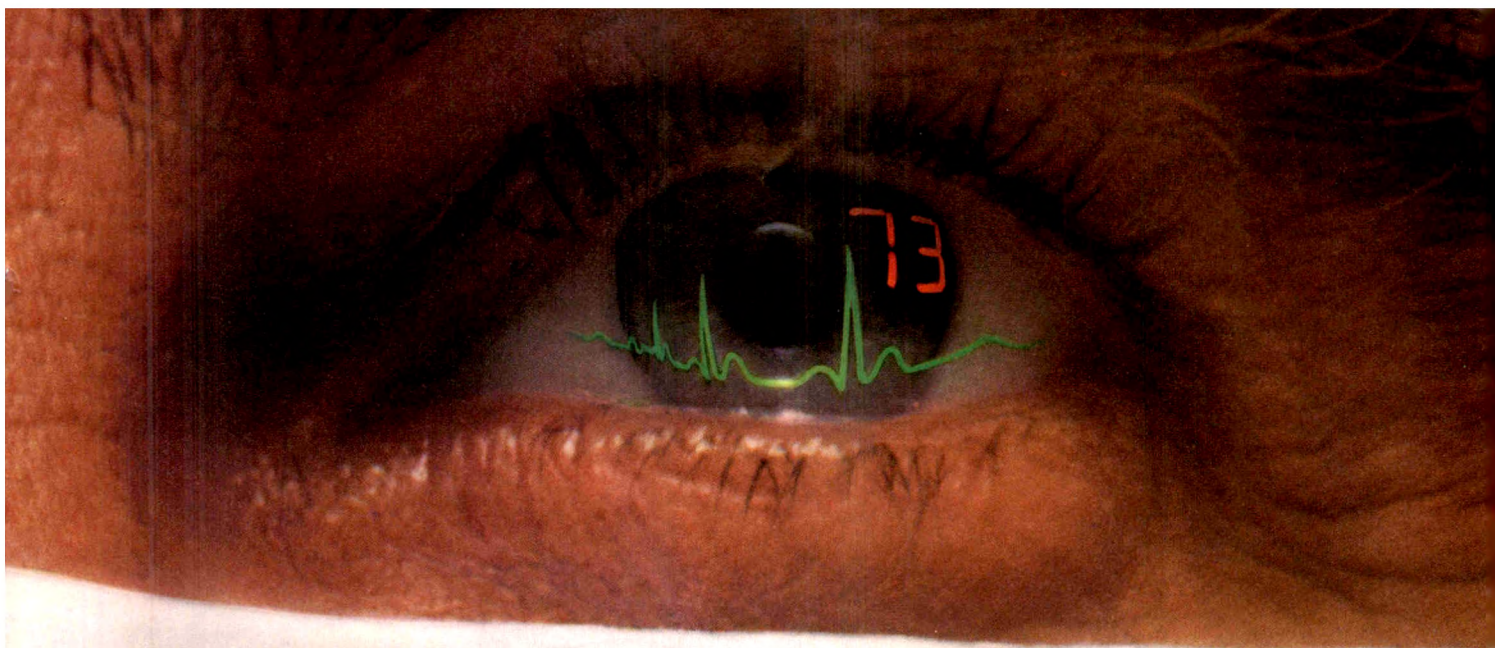


Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED₉₅.⁵

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.⁵

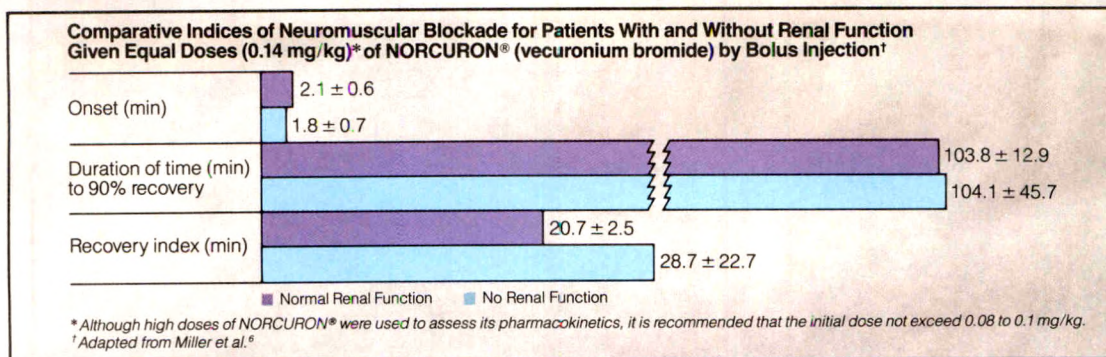
The Effect of Nondepolarizing Muscle Relaxants*				Percent of Control		
Drug	Dose (mg/kg)	xED ₉₅	Histamine	Mean Arterial Pressure	Heart Rate	
Tubocurarine	0.5	1	410	78	116	
Metocurine	0.5†	2	212	79	119	
Atracurium	0.6†	3	192	80	108	
Vecuronium	0.1	1.7	117	100	99	
Vecuronium	0.2	3.5	87	99	102	

*Adapted from Basta et al.⁵
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.⁶

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.⁶



**The surgical muscle relaxant
ideal for virtually all patients
including those at risk.**

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. 2. Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. 3. Krieg N, Crul JF, Booi LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of

vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. 5. Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. 6. Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide)*. Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2R,3R,5a,16b,17b)-3,17-bis(acetyloxy)-2-[(piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED₅₀ (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalational anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g., pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 55-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-45 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose (1.028 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebation. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin), tetracyclines, bacitracin, polymyxin B, colistin, and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalational anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution

5% glucose in saline

Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC #0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only, DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC #0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS. Manufactured for ORGANON INC. by BEN VENUE LABORATORIES, INC., Bedford, OH 44146. ISSUED 5/86.



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Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

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Annual Dues for Educational Members: One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

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Associate Membership (_____)
Educational Membership (_____)

Please print clearly: _____
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Street Address

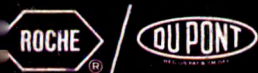
City, State, Zip Code (country)

VERSED

nidazolam HCl/Roche [®] IV

INSTEAD

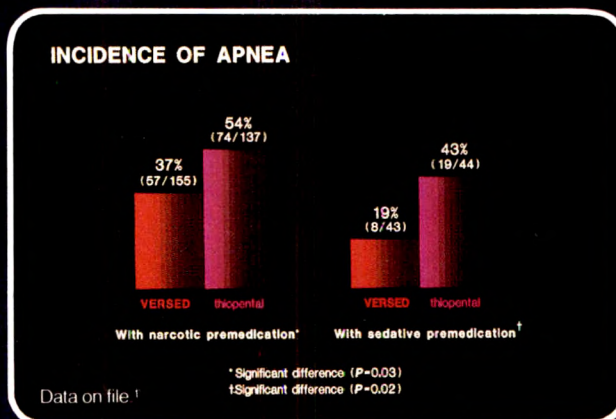
...of thiopental



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Key advantages in induction

- **Significantly less apnea**



- **Better hemodynamic stability**

While differences were not statistically significant, VERSED I.V. produced less pronounced decreases in stroke volume, heart rate, cardiac output and systemic vascular resistance...and a less pronounced increase in mean right atrial pressure²

- **Pronounced anterograde amnesia**

Significantly more VERSED-treated patients (24/24) had complete or partial anterograde amnesia than did thiopental-treated patients (13/26)¹

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and familiar with all dosing and administration guidelines. Reduce dosage in elderly and debilitated, in patients receiving narcotic premedication, and in those with limited pulmonary reserve.

New

the dilution
you've been
requesting—

1 mg/mL

for easier
titration,
easier
administration



INJECTABLE

VERSED®

brand of
midazolam HCl
equivalent to 1 mg/mL and 5 mg/mL

Roche 

A significant advance in anesthetic induction

Please see references and summary of product information on the following page.

References: 1. Data on file (Doc. #069-005, 007), Roche Laboratories
2. VERSED® (brand of midazolam HCl/Roche) @ Scientific Summary.
Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley,
NJ, 1986

**VERSED®
(brand of midazolam HCl/Roche) @
INJECTION**

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: IM: preoperative sedation, to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents, as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma, may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen and resuscitative equipment for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia, cardiac arrest unless effective countermeasures are taken immediately. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs.
Guard against unintended intra-arterial injection, hazards in humans unknown.
Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not.
Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.
Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.
Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.
PRECAUTIONS: General. Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by about 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.
VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.
VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.
Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication. A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

VERSED® (brand of midazolam HCl/Roche)

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted. A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects. Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred. (See WARNINGS.) In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic clonic movements and muscle tremor), hyperactivity and combativeness have been reported. (See DOSAGE AND ADMINISTRATION.)

Following IM injection: headache (13%), local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%), local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: **Respiratory:** Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. **Cardiovascular:** Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. **Gastrointestinal:** Acid taste, excessive salivation, retching. **CNS:** Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. **Special Sense:** Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. **Integumentary:** Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. **Miscellaneous:** Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients. (See WARNINGS.) **IM use:** Inject deep in large muscle mass. **IV use:** Administer initial dose over 20 to 30 seconds for induction of general anesthesia. For conscious sedation administer initial dose over 2 to 3 minutes. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.



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P I 0387

Eye Guard™

Patent Pending

- Protects patient's eyes from contact with drapes
- Shields patient's eyes from debris or accidental injury
- Seals to promote a 'Greenhouse' effect to keep eyes moist

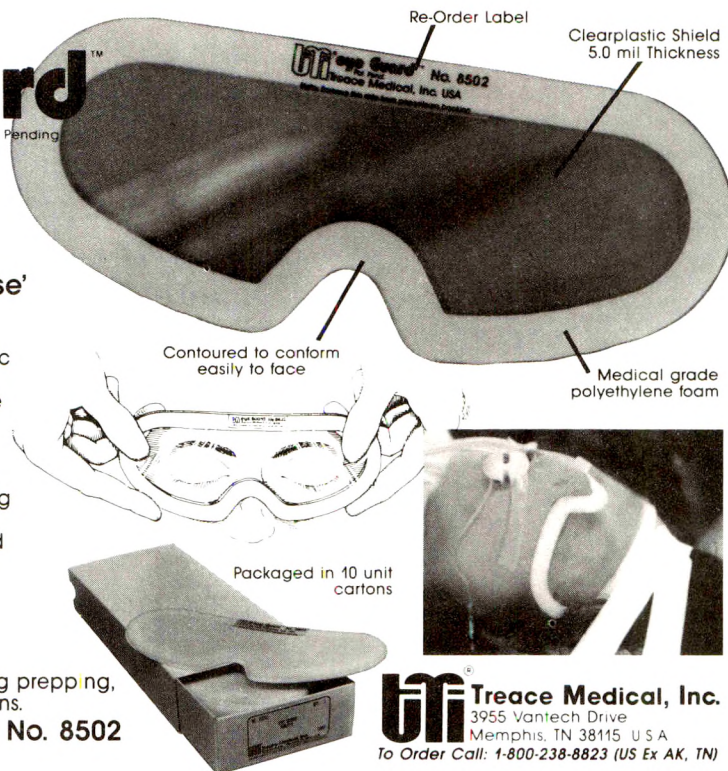
Eye Guard is a full 5.0 mil thick clear plastic shield, backed with a soft medical grade foam and non-irritating adhesive to adhere to the face and enclose the eyes.

Eye Guard is the ideal eye protector for surgical patients, allowing visualization for patient monitoring, and when administering anesthesia with a mask, prevents anesthesia gas from contacting eyes. Eye Guard minimizes the risk of accidental eye injury when placing or moving drapes or instruments and from debris. Also, Eye Guard creates a 'greenhouse' effect, keeping the eyes moist during longer procedures.

Eye Guard is non-sterile and applied during prepping, prior to draping. Packaged in 10 unit cartons.

Pak/10 No. 8502

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For outpatient anesthesia



Rapid

Well-suited to the rapid turnover of outpatient cases, the low solubility of isoflurane in blood and tissue (only that of nitrous oxide is lower) enables you to quickly adjust the level of anesthesia to patient and surgical requirements.

Following anesthesia, a rapid washout and prompt recovery provide for your early patient assessment. Patient alertness and cooperation can facilitate handling in the outpatient setting.

Complete

Without any other agent or premedicant, isoflurane provides every action required for a complete anesthetic, on a closely controlled, breath-by-breath basis: unconsciousness, surgical analgesia, amnesia, and good surgical muscle relaxation—a useful advantage for laparoscopies and orthopedic work, and one that begins when the anesthetic begins and ends with elimination of the anesthetic, thereby decreasing the risk of residual paralysis in the PAR.

Because isoflurane is a complete anesthetic when given alone in oxygen or room air, nitrous oxide can be eliminated if you choose. Isoflurane anesthetics are seldom complicated and prolonged by postoperative nausea and vomiting.

FORANE[®] (isoflurane, USP)



Excellent Safety Profile

Stability of heart rhythm and good cardiac output are notable features of an isoflurane anesthetic. CNS excitation does not occur at any concentration or PaCO_2 level. Virtually 100 % of isoflurane is exhaled unchanged from the patient (only 0.17 % of the isoflurane taken up is recovered as metabolites). This near absence of metabolic by-products all but assures an absence of hepatic or renal toxicity from metabolism.

Anaquest



For outpatient anesthesia

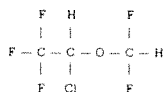
FORANE® (isoflurane, USP)

Rapid...Complete...Excellent Safety Profile

CAUTION Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

FORANE (isoflurane, USP) is a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether and its structural formula is



Some physical constants are

Molecular weight	184.5
Boiling point at 760 mm Hg	48.5 °C (uncont.)
Refractive index n_D^{20}	1.2990-1.3005
Specific gravity 25 °/25 °C	1.496
Vapor pressure in mm Hg**	20 °C 138 25 °C 196 30 °C 267 35 °C 350

**Equation for vapor pressure calculation

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where} \quad A = 8.056$$

$$B = -1664.58$$

$$T = ^\circ\text{C} + 273.16 \text{ (Kelvin)}$$

Partition coefficients at 37 °C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	9.6

Partition coefficients at 25 °C - rubber and plastic

Conductive rubber/gas	2.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	1.00
Polyethylene/gas	2.0
Polyurethane/gas	4.4
Polyolefin/gas	1
Butyl acetate/gas	2.5

Purity by gas chromatography

Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec and 23 °C	None
--	------

Lower limit of flammability in oxygen or nitrous oxide at 300 joules/sec and 23 °C

	Greater than usual
--	--------------------

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, etheral odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 20 hours to a 2 amp, 115 volt, 60 cycle long wave UV light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methacrylate-methanol solution, a strong base, for over six months consumed essentially no alkali; indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows

Age	100 % Oxygen	70 % N ₂ O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed readily with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a high response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO₂, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O.

See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (not canister). PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte fluid and base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiological effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using

- vaporizers calibrated specifically for isoflurane,
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

$$\% \text{ isoflurane} = \frac{100 F_V F_V}{F_T (P_A - P_V)}$$

where P_A = Pressure of atmosphere
 P_V = Vapor pressure of isoflurane
 F_V = Flow of gas through vaporizer (mL/min)
 F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0 % isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5 % concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0 % may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0336

Revised 10-85

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Generation of Halothane-Induced Immune Response in a Guinea Pig Model of Halothane Hepatitis

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SIADAT-PAJOUH M, HUBBARD AK, ROTH TP, GANDOLFI AJ. Generation of halothane-induced immune response in a guinea pig model of halothane hepatitis. *Anesth Analg* 1987;66:1209-14.

A guinea pig model of halothane hepatitis was used to explore the humoral immune response induced by multiple halothane exposures and the potential role this response might play in contributing to liver damage. Three different strains of guinea pigs (Strain 2, Amana, and Hartley) were exposed to 1% halothane under either 21 or 80% oxygen for 4 hr at 2-week intervals. In each strain, halothane induced the appearance of an antibody cross-reactive with trifluoroacetylated guinea pig serum albumin (TFA-GSA). Three of six Strain 2 guinea pigs demonstrated an association between antibody titer and serum glutamate pyruvate transaminase levels. However, the possible cause and effect

relationship between these two factors requires more investigation. Hartley guinea pigs had a 4- to 11-fold higher level of anti-TFA antibody than the other two strains because of either a "higher responder" genetic background or exposure conditions that favored oxidative metabolism of halothane. Immunization of Amana guinea pigs with TFA-GSA evoked a specific anti-TFA antibody response. However, the presence of this antibody before halothane exposure did not potentiate the transient liver damage induced by exposure. Thus, these results demonstrate that in guinea pigs multiple exposures to halothane induce the formation of an antibody that recognizes a reactive intermediate of halothane formed during the anesthetic's metabolism.

Key Words ANESTHETICS, VOLATILE—halothane. LIVER—hepatotoxicity. IMMUNE RESPONSE—antibodies.

Recent studies have focused on investigating a role for the immune system in mediation of halothane-induced hepatitis. Although epidemiologic data suggest that the induced hepatic injury seen in humans might result from a hypersensitivity response to modified self-components in the liver (1), convincing evidence of sensitization to halothane metabolic intermediates has been difficult to obtain. Early investigation demonstrated that a biotransformation intermediate of halothane could bind covalently to liver macromolecules, thereby serving as a hapten to alter the antigenicity of hepatocyte membrane proteins (2). The reactive metabolic intermediates of halothane responsible for modifying self-components in the hepatocyte membrane could include, among others, a trifluo-

roacetyl halide (TFA) from the oxidative pathway, free radicals, or carbene intermediates from reductive pathways (3).

Investigators have for some time used animal models to examine sensitization to the halothane reactive intermediate, TFA, and the role such sensitization might play in exacerbating halothane-induced liver damage. Rosenberg and Wahlstrom (4) first noted that TFA conjugated to carrier proteins could induce an antibody response in rabbits. Mathieu et al. (5,6) also found that when guinea pigs were injected with TFA-guinea pig serum albumin (GSA), an antibody response (humoral immunity), as well as a delayed type hypersensitivity response (cell-mediated immunity) was produced. The TFA moiety, then, could serve as a hapten in the initiation of an immune response. In addition, these investigators initiated studies to determine if sensitivity to a TFA-carrier protein could exacerbate halothane-induced liver damage (7). Although no correlation could be found between a cell-mediated immune response and liver damage, an inverse correlation existed between antibody titers and markers of liver damage, indicating possible protection by a humoral immune response. Other investi-

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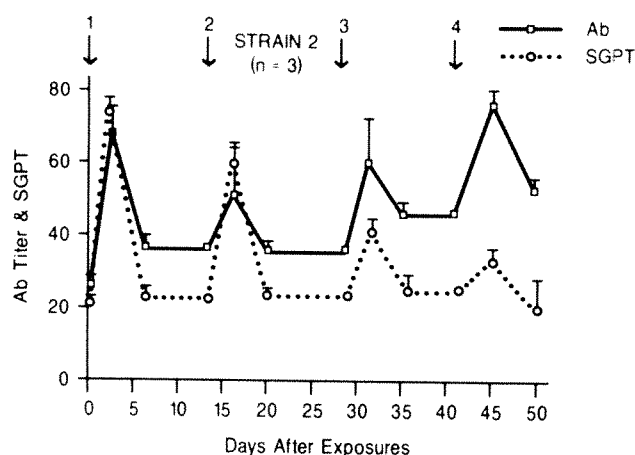


Figure 1. Halothane-induced antibody and SGPT levels in responding Strain 2 guinea pigs. Six Strain 2 guinea pigs were exposed to 1% halothane in 21% oxygen four times at 2-week intervals. Only three survived the duration of the experiment. The reciprocal of the antibody dilution, which yields an optical density of 0.3, is used for quantitation of antibody in an ELISA ($\square$). The SGPT values are expressed in Wroblewski Ladue units ($\circ$). The arrows show the time for each halothane exposure. Each point represents the mean $\pm$ SE of three animals.

gators later confirmed the fact that immune cell sensitization to TFA-carrier protein complex did not exacerbate halothane-induced liver damage in guinea pigs (8) or rats and mice (9).

Previous work in our laboratory with rabbits documents the induction by halothane of a humoral immune response that reacted with TFA-carrier protein (10,11). The intensity of this antibody response was dependent on the oxygen tension during readministrations of halothane (11). There was, however, no association between the induction of this immune response in rabbits and any markers of liver damage. Consequently, a guinea pig model of halothane-induced liver damage was developed in our laboratory. Lind et al. (12) reported halothane-induced liver injury in both sexes of either Hartley, Amana, Strain 2, or Strain 13 guinea pigs. Current studies, using the exposure conditions described by Lind (1% halothane, 4-hr exposure), explore the induction of a humoral immune response by multiple halothane exposures and the potential role this response may play in contributing to liver damage.

Methods

Study Animals

Nine adult female Amana (outbred), 6 adult male Strain 2 (inbred) (University of Arizona breeding colonies), and 20 adult female Hartley (outbred) guinea pigs (Harlan Sprague-Dawley Inc., Indianapolis, IN) each

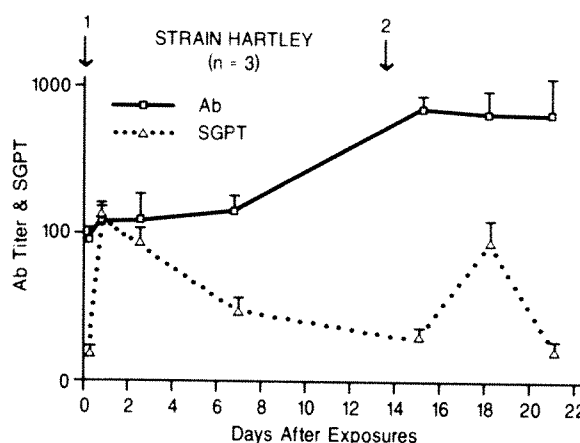


Figure 2. Halothane-induced antibody and SGPT levels in Hartley guinea pigs. Hartley guinea pigs were exposed to 1% halothane in 80% oxygen two times at 2-week intervals. Of the 20 Hartley guinea pigs, 18 were exposed and 9 were killed after the first exposure and 9 after the second exposure. Two guinea pigs remained unexposed to determine background antibody and SGPT levels. Each point represents the mean $\pm$ SE of three animals. The reciprocal of the antibody dilution, which yields an optical density of 0.3, is used for quantitation of antibody in an ELISA ($\square$). The SGPT values are expressed in Wroblewski Ladue units ($\triangle$). The arrows indicate the time of exposure.

weighing approximately 660 g were housed in the University of Arizona Division of Animal Resources and fed food and water ad libitum.

Synthesis of Trifluoroacetyl-Guinea Pig Serum Albumin

Ethyl thioltrifluoroacetate (Pierce Chemical Co., Rockford, IL) was reacted with lysine residues on guinea pig serum albumin (GSA) (Sigma Chemical Co., St. Louis, MO) to produce trifluoroacetylated guinea pig serum albumin (TFA-GSA) (13). The conjugated TFA-GSA was dialyzed in water for 2 days at 4°C and subsequently lyophilized. The protein content of the conjugate was determined by the Lowry protein assay (14), and the ratio of free lysine to TFA-bound lysine (80–85%) was also assessed (15).

Guinea Pig Halothane Exposures

Strain 2 guinea pigs were exposed four times at 2-week intervals to 1% halothane in 21% oxygen and 88% nitrogen for 4 hr. The animals were subsequently bled on Days 3 and 7 after each exposure. Venous blood was obtained from all guinea pigs through the nail vein with the aid of a vacuum bleeding apparatus to enhance blood flow and cause minimal stress during repetitive blood sampling (16). Of 18 Hartley guinea pigs exposed to 1% halothane (80% oxygen), 9 were

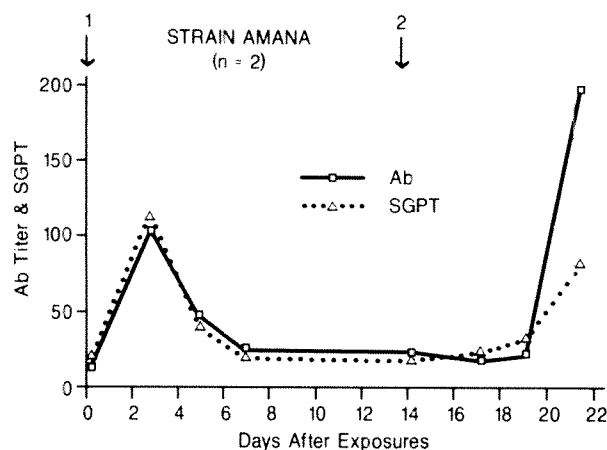


Figure 3. Halothane-induced antibody and SGPT levels in Amana guinea pigs. Nine Amana guinea pigs were exposed to 1% halothane in 80% oxygen two times at a 2-week interval. Only two survived the duration of the experiment. The reciprocal of the antibody dilution, which yields an optical density of 0.3, is used for quantitation of antibody in an ELISA ($\square$). The SGPT values are expressed in Wroblewski Ladue units (Δ), and the arrows represent the time of each exposure. Each value is the mean of two animals.

killed after one exposure (three on either Days 1, 3, or 7) and 9 others were killed after two exposures (three on either Days 1, 3, or 7). Amana guinea pigs (immunized or nonimmunized) were exposed twice to 1% halothane, 80% oxygen for 4 hr at 2-week intervals. The animals were bled on Days 3, 5, and 7 after each exposure. During all exposures, halothane concentration in the Plexiglas exposure chamber was monitored by gas chromatography and the oxygen concentration measured with an oxygen electrode (17).

Immunization of Guinea Pigs with TFA-GSA

Two milligrams TFA-GSA emulsified in 0.5 ml water and 1.5 ml of Freund's complete adjuvant (Difco Lab., Detroit, MI) were injected in the legs (intramuscularly) and back (subcutaneously) of four Amana guinea pigs. One booster immunization was repeated 3 weeks later. Antibody titers were monitored by an enzyme-linked immunosorbent assay (ELISA) on plasma samples.

Enzyme-Linked Immunosorbent Assay

The presence and titer of antibodies specific for or cross-reactive with TFA-GSA were assessed using the ELISA as previously described by Callis et al. (11). ELISA plates (Costar, Cambridge, MA) were coated with TFA-GSA (5.0 μ g/well) in 0.5 M sodium carbonate buffer and incubated overnight at 4°C. The next day, plates were washed with 0.01 M phosphate-buffered saline (PBS)-0.5% Tween 20 and incubated

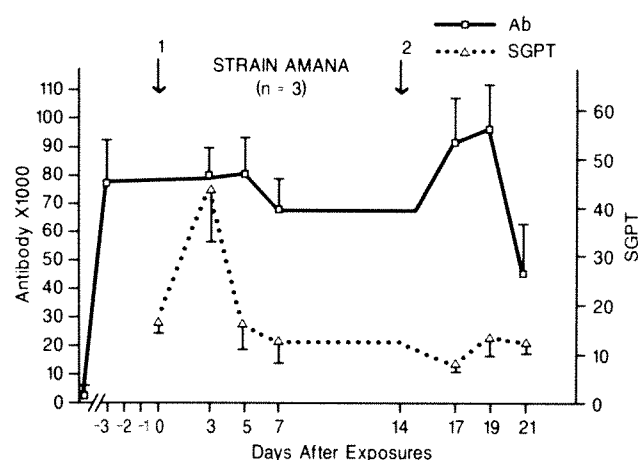


Figure 4. Effect of preexisting anti-TFA antibody on toxicity. Four Amana guinea pigs were given a primary immunization and booster of TFA-GSA followed by two exposures to 1% halothane under 80% oxygen. Only three survived the duration of the experiment. The reciprocal of the antibody dilution, which yields an optical density of 0.5, is used for quantitation of antibody in an ELISA ($\square$). The SGPT values are expressed in Wroblewski Ladue units (Δ), and the arrows represent the time of each exposure. Each value is the mean $\pm$ SE of three animals.

with a 3% gelatin solution (J.T. Baker, Phillipsburg, PA) for 1 hr at 37°C. After another wash, serial two-fold dilutions of plasma were added and after a 1-hr incubation, HRP-conjugated goat anti-guinea pig immunoglobulin (Cooper Biomedical Laboratories, Malvern, PA) in 0.5% gelatin was added for another 1-hr incubation. The plates were again washed with PBS-Tween and the substrate for the peroxidase, 2,2'-azinobis(3-ethylbenzthiazoline sulfonic acid) (Sigma Chemical Co.), was added. The reaction was terminated with 5% sodium dodecyl sulfate (Sigma Chemical Co.). The degree of antibody binding was determined using a Titertek ELISA reader (Flow Laboratories, McLean, VA) with monitoring at 410 nm and a 490-nm reference wavelength. For quantitation of antibody in the ELISA, the reciprocal of the antibody dilution that gave an optical density of 0.300 (Figs. 1, 2, 3, 5) or 0.500 (Fig. 4) was used.

Measurements of Hepatic Damage

Levels of serum glutamate pyruvate transaminase (SGPT) were measured as a systemic marker of hepatocyte damage using commercial kit No. 5910 (Sigma Chemical Co.).

Data Presentation

Data are expressed as the mean $\pm$ SE of three or four animals.

Results

Halothane-Induced Antibodies in Strain 2 Guinea Pigs

Multiple (four) halothane exposures induce in three of six exposed Strain 2 guinea pigs an antibody that recognized TFA-GSA. Data for the three responding animals are presented in Figure 1. Elevations in levels of SGPT were also observed in these animals, indicating hepatocellular damage by halothane. The peak of both antibody response and SGPT levels in these animals occurred on the third day after each exposure with a subsequent decline by Day 7. The chronology of these two measurements suggests an association between the presence of antibody and increased SGPT levels.

Halothane-Induced Antibodies in Hartley Guinea Pigs

Two halothane exposures of Hartley guinea pigs also resulted in the generation of an antibody that was reactive with TFA-GSA (Fig. 2). The concentration of halothane-induced antibody was higher after the second exposure than after the first, indicating the possible induction of a secondary immune response. In addition, the first halothane exposure of these Hartley guinea pigs caused an elevation in SGPT levels on Days 1 and 3, whereas exposure 2 caused elevated SGPT levels on Day 3 only. There appears to be a slight association between the elevation in levels of antibody and SGPT after this second exposure to halothane.

Halothane-Induced Antibodies in Amana Guinea Pigs

Exposure of an Amana guinea pig to halothane also induced an anti-TFA antibody response that peaked on Day 3 after the first exposure and on Day 7 after the second exposure (Fig. 3). A similar chronology was observed between elevations in antibody and SGPT, because levels of SGPT were also elevated on Day 3 after the first exposure and on Day 7 after the second exposure.

The Effect of Preexisting Anti-TFA Antibodies on Halothane Hepatotoxicity

To determine if the transient liver damage seen after exposure to halothane could be perpetuated after subsequent exposures, Amana guinea pigs were immu-

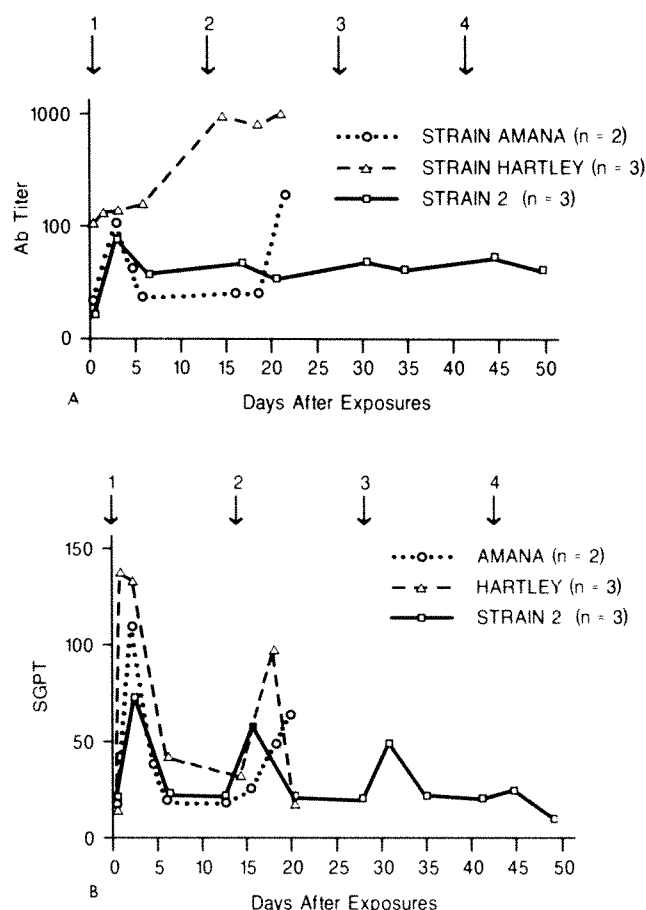


Figure 5. Strain differences in halothane-induced antibody and toxicity. (A) Levels of anti-TFA antibody using the same log scale of antibody titer were compared in three strains of guinea pigs (Amana, $\circ$; Hartley, Δ ; and Strain 2, $\square$). The arrows denote time of halothane exposure. (B) Levels of SGPT were compared in three strains of guinea pigs (Amana, $\circ$; Hartley, Δ ; and Strain 2, $\square$). The arrows denote time of halothane exposure.

nized with TFA-GSA before two exposures to halothane (Fig. 4). Immunization of three Amana guinea pigs with TFA-GSA resulted in the induction of a specific anti-TFA antibody response indicating that TFA-GSA was immunogenic. Antibody levels 1 month after immunization evidenced titers from 60,000 to 120,000. The subsequent challenge of these immunized Amana guinea pigs with two exposures to halothane (80% oxygen) resulted in an apparent secondary antibody response after the second exposure. Although one of the guinea pigs showed an elevation in SGPT levels after halothane anesthesia, no association was observed between the SGPT values and antibody titer in this animal. Thus, it appears that preexisting anti-TFA antibodies did not potentiate halothane hepatotoxicity.

Discussion

The present studies indicate that multiple halothane exposures in guinea pigs result in the induction of a humoral immune response to a reactive intermediate formed during halothane metabolism, the trifluoroacetyl halide moiety. Moreover, the levels of anti-TFA antibody are compared in all three strains with regard to the degree (log titer) and chronology of this immune response (Fig. 5A). The peak of halothane-induced antibody generated in Strain 2 guinea pigs occurred on the third day following the first exposure, whereas in Strain Amana and Strain Hartley guinea pigs, a higher antibody response followed the second halothane exposure. The magnitude of the immune response in Hartley guinea pigs was greater (peak titer of 900) than in either Strain 2 (peak titer of 80) or Amana guinea pigs (peak titer of 200). This elevated response in Hartley animals may be due to genetically determined traits such as increased metabolism of halothane and hence more TFA-immunogen or to increased immune responsiveness (18). The latter seems more appropriate in explaining the differences in antibody titer between Amana and Hartley guinea pigs, because both strains were exposed to halothane under the same conditions (e.g., oxygen tension). Alternatively, the increase in antibody titer may be due to increased oxygen tension (21% in the Strain 2 animals; 80% in the Hartley strain), because increased oxygen tension in rabbits exposed to halothane resulted in substantially elevated anti-TFA antibody levels (11). Exposure to halothane under conditions favoring oxidative metabolism would be preferential for the generation of the immunogen, TFA-carrier protein, thereby eliciting more anti-TFA antibody. Whether the appearance of this antibody is the cause of hepatotoxicity or the result is still under investigation.

Hughes and Lang (19) first reported the guinea pig as a potential animal model for studying halothane-induced liver injury. They found that exposure of Dunkin-Hartley guinea pigs multiple times at 2-week intervals produced focal hepatic lesions in 7 of 50 guinea pigs. Lunam et al. (20) later confirmed these studies by a single exposure to halothane of an outbred strain of guinea pig. They noted that animals developed hepatic necrosis within 2 or 3 days but recovered fully by the seventh day. Moreover, these investigators suggest that the genetic predisposition of the guinea pigs is an important determinant in their susceptibility to halothane liver damage (21). In addition, Lind et al. (12) observed that Strain 2 guinea pigs (inbred) developed a more severe hepatic lesion upon a single halothane exposure than did Amana (outbred)

or Hartley (outbred) strains. Thus, the rationale for exploring the anti-TFA antibody response in three different strains of guinea pigs was based on the observations that some strains of guinea pigs were more responsive in halothane-induced liver damage than were other strains. Because immune responsiveness is also genetically determined (18), experiments were designed to determine if there was an association between the pathologic and antibody response in these "higher" responders. Although all exposed guinea pigs were susceptible to the chemotoxic injury of halothane as evidenced by transient increases in levels of SGPT after each exposure (Fig. 5B), only Strain 2 animals showed an association between peaks in antibody and SGPT levels (Fig. 1). In addition, Hartley guinea pigs evidenced higher anti-TFA antibody titers (Fig. 5A) and SGPT levels (Fig. 5B) over time than the other two strains. There was, however, no chronological association between these responses as seen in Strain 2 animals. In fact, in the Strains Amana and Hartley, as antibody titers increase after Exposure 2, levels of SGPT decrease. Although one might postulate a "protective" role for this antibody, such interpretation is speculative.

Immunization of Amana guinea pigs with TFA-GSA resulted in the generation of a specific anti-TFA-GSA antibody response indicating the potential immunogenicity of TFA complexed to carrier proteins. The capacity of TFA-carrier protein antigens to induce an antibody response was first noted by Rosenberg and Wahlstrom (4) and most recently by Satoh et al. (22) and Callis et al. (11). In this last report, rabbits immunized with trifluoroacetylated-rabbit serum albumin (TFA-RSA) developed a specific anti-TFA-RSA antibody that declined in titer fairly rapidly over time because of its low degree of immunogenicity. One would expect the same decline in antibody titer in immunized guinea pigs as well. A single exposure of these immunized guinea pigs, however, caused the sustainment of this anti-TFA antibody response, and a second halothane exposure caused elevation in the antibody titer. It appeared that halothane exposure induced an immunogen highly cross-reactive with TFA-GSA, thereby causing the clonal expansion of T and B cells previously sensitized by immunization with TFA-GSA (23). Although halothane exposure induced, in a nonimmunized Amana guinea pig, a transient hepatotoxicity, this toxicity could not be potentiated by the presence of anti-TFA antibodies before halothane exposure. This result was also seen in rabbits immunized with TFA-RSA before halothane exposure (11) as well as in reports by others (8,9). The failure of this specific anti-TFA antibody to exacerbate

liver damage may be due to inducing a population of antibodies with an appropriate specificity for hepatocyte membrane proteins or to evaluating too few or too insensitive markers of hepatic damage.

The induction of an antibody response that can react with a synthetic hapten-carrier complex, TFA-GSA, by single or multiple halothane exposures in guinea pigs, suggests that the halothane-induced immunogen is probably comprised of a TFA moiety conjugated to a modified self-hepatocyte protein. Although a slight association was observed between the presence and titer of this halothane-induced antibody and a marker of liver damage (SGPT), the potential of this antibody in mediating liver damage is still under investigation. This work clearly demonstrates, however, that multiple halothane exposures in any of three strains of guinea pigs result in the generation of an antibody response to a reactive intermediate of halothane. Subsequent work will focus on studying the interaction between this anti-TFA antibody and halothane-exposed hepatocytes as well as further characterization of this halothane-induced immunogen.

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Age Predicts Effective Epidural Morphine Dose after Abdominal Hysterectomy

L. Brian Ready, MD, FRCP(C), H. S. Chadwick, MD, and Brian Ross, MD

READY LB, CHADWICK HS, ROSS B. Age predicts effective epidural morphine dose after abdominal hysterectomy. *Anesth Analg* 1987;66:1215-8.

To determine whether there is a relation between patient age and the effective dose of epidural morphine for relief of incisional pain after abdominal hysterectomy, experience treating 66 patients between the ages of 22 and 84 years was retrospectively examined. Linear regressions were plotted for age vs effective 24-hr morphine dose, age vs pain at rest, and age vs pain during coughing. To evaluate the frequency of side effects, the population was classified into three age groups (<40, 40-60, >60 yr) and examined by Fisher's exact test for possible differences. Although there was wide interpatient variability, there was a correlation between pa-

tient age and effective 24-hr morphine dose ($r = -0.40$, $P < 0.01$). The relation is described by the following equation: 24-hr morphine dose (mg) = $18 - \text{age}(0.15)$. The quality of analgesia did not diminish with the smaller doses administered to the older patients. The frequency of side effects did not differ significantly in the three age groups. These observations may be related to higher CSF morphine concentrations or to a greater analgesic effect from morphine absorbed systemically from the epidural space in older patients.

Key Words: PAIN—postoperative. AGE—postoperative pain. ANESTHETIC TECHNIQUES, EPIDURAL—morphine.

Among many reports attesting to the efficacy and advantages of epidural narcotics for controlling pain after major abdominal surgery, there is little information available regarding predictors of effective doses for individual patients. Gustafsson et al. (1) found higher CSF concentrations of morphine in older patients than in younger patients given the same epidural morphine dose. However, it has not been determined whether the effective epidural morphine dose after surgery is related to patient age.

It has become routine at our hospital for anesthesiologists to manage postoperative pain after major gynecologic surgery. In this paper, using data collected during daily postoperative visits, we document a relation between age and effective epidural morphine dose in patients we treated after abdominal hysterectomy.

Methods

With the approval of our institutional human investigation committee, a retrospective examination was

undertaken of 66 consecutive patients in whom postoperative pain after abdominal hysterectomy was treated with epidural morphine by our anesthesiology-based pain management service. All pertinent information during the course of treatment was collected on specially designed patient care sheets, checked for completeness, entered in a computer database, then retrieved and evaluated at a later time for this investigation. For their operative procedures this group of patients had continuous lumbar epidural anesthesia with 2% lidocaine or 0.5% bupivacaine with or without light general endotracheal anesthesia (60% N₂O and/or approximately 0.5 MAC of isoflurane, enflurane, or halothane) according to the preference of the patient and anesthesiologist. Appropriate segmental sensory anesthesia to pinprick was used to confirm correct epidural catheter placement in all patients before surgical incision or induction of general anesthesia. Narcotics, antiemetics, and antihistamines were avoided as premedicants and as intraoperative supplements.

On the basis of our earlier clinical experience (2), the initial dose of undiluted preservative-free epidural morphine (a 0.1% solution of Duramorph, A. H. Robins) was determined by patient age (15-44 yr, 5 mg; 45-65 yr, 4 mg; 66-75 yr, 3 mg; over 75 yr, 2 mg). The first dose was administered by the operating room

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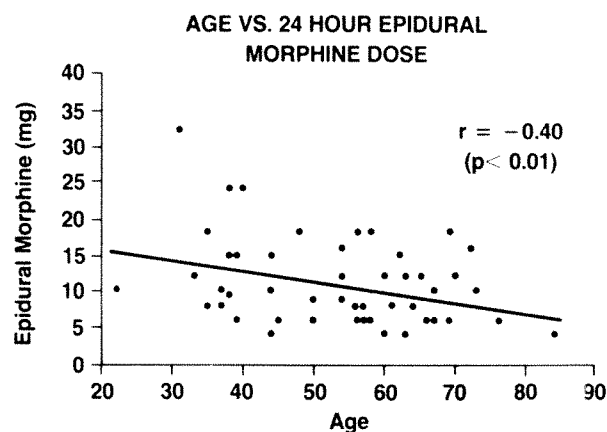


Figure 1. There is a statistically significant ($P < 0.01$) negative correlation between age and effective 24-hr epidural morphine dose after abdominal hysterectomy. The relation can be described by the following equation: 24-hr epidural morphine dose (mg) = $18 - \text{age}(0.15)$.

anesthesiologist 1 hr before the expected completion of surgery. The anesthesiology team assigned to post-operative pain management (in our hospital known as the Acute Pain Service) was notified and thereafter assumed responsibility for providing analgesia. In the recovery room, adequacy of analgesia was assessed when the local anesthetic block receded. Subsequent morphine doses and intervals between epidural injections were adjusted as needed for each patient to establish a pain-free or nearly pain-free state at rest, the ability to cough effectively and ambulate without severe pain, all with minimal side effects. Although the initial epidural morphine dose was determined by age, subsequent doses and intervals between injections were established by titration until the desired therapeutic effect was achieved and were thus not predetermined by age.

Treatment with epidural morphine was continued until a fluid diet was prescribed by the surgeon and incisional pain could be effectively controlled by an oral analgesic.

For this report we considered the following information: 1) age of patient; 2) effective 24-hr epidural morphine dose (24 divided by the injection interval in hours multiplied by the number of milligrams of morphine given at each injection); and 3) patient estimates of incisional pain 24 hr after surgery at rest and during a vigorous cough using a 0–10 verbal pain scale (0 = no pain; 10 = most severe pain imaginable; pain-free was defined as 0 and nearly pain-free as 1 or 2 on this scale).

Linear regressions by the method of least squares were plotted for age vs effective 24-hr epidural drug dose, age vs pain at rest, and age vs pain while coughing.

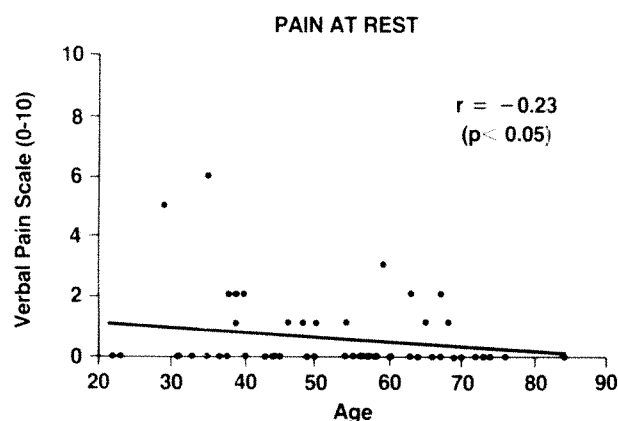


Figure 2. There is a weak but statistically significant ($P < 0.05$) negative correlation between age and severity of pain at rest after abdominal hysterectomy.

To evaluate the frequency of side effects, the population was classified into three age groups (<40, 40–60, >60 yr) and was examined by Fisher's exact test for possible differences.

Duration of treatment with epidural morphine in each age group was tested for statistical significance by one-way analysis of variance.

Results

Observations from 66 consecutive patients who had undergone abdominal hysterectomy and had received epidural morphine were reviewed. Ages ranged from 22 to 84 years with a mean age $\pm$ SD of 51.7 ± 14.6 yr. The mean dose of epidural morphine per injection was 4.4 ± 1.5 mg (range 2–8), and the mean interval between injections was 10.1 ± 2.0 hr (range 6–12). The mean 24-hr epidural morphine dose requirement was 11.1 ± 5.3 mg (range 4–32).

Figure 1 shows the correlation between age and effective 24-hr morphine dose ($r = -0.40$, $P < 0.01$). The relation can be described by the following equation: 24-hr morphine dose (mg) = $18 - \text{age}(0.15)$.

The patients' analgesia scores are plotted as a function of age in Figures 2 and 3. There is a weak but statistically significant ($P < 0.05$) negative correlation between age and severity of pain at rest. The correlation remains negative but is not statistically significant during coughing.

Table 1 lists the frequency of side effects and length of treatment with epidural morphine for the age groups <40, 40–60, and >60 yr. There are no significant differences in the three groups in relation to these observations.

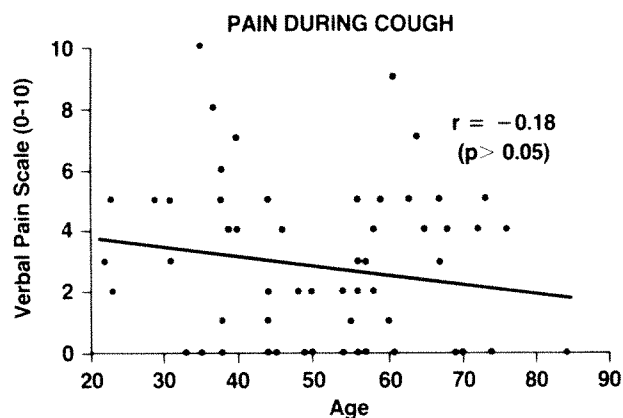


Figure 3. There is a trend that does not reach statistical significance suggesting the possibility that increasing age is associated with less pain during coughing after abdominal hysterectomy.

Discussion

Although it is recognized that there is wide interpatient variability with regard to effective dose of morphine when injected epidurally for the relief of postoperative pain, little information is available to guide clinicians in making a dose selection for individual patients. Our clinical practice in the use of epidural narcotics for management of postoperative pain includes adjustment of drug doses and injection intervals to meet the needs of each individual patient. The therapeutic goal is to produce a pain-free or nearly pain-free state with minimal side effects. Figure 1 shows that in the population we studied there is an inverse relation between effective 24-hr epidural morphine dose and patient age. On the basis of our earlier experience with epidural narcotic dose requirements (2), and published reports that older patients may be at higher risk of delayed respiratory depression after administration of epidural narcotics (3), we considered it necessary to reduce initial morphine doses for older patients. Subsequent doses and intervals between injections were adjusted for each patient to achieve our therapeutic goal. The fact that quality of analgesia did not diminish but rather improved with the smaller doses administered to the older patients supports the validity of the age-dose relation we have observed.

Although the relation between epidural morphine requirement and age is statistically significant, considerable interpatient variability is present. This might be in part explained by other determinants of effective dose such as body weight and prior narcotic tolerance. Wide interpatient variability in the effective dose of intramuscular narcotics is also reported (4).

The administration of epidural morphine produces analgesia by two mechanisms—an effect at opioid re-

Table 1. Incidence of Side Effects and Duration of Treatment

	Age groups (yr) ^a		
	<40 (n = 17)	40-60 (n = 27)	>60 (n = 22)
Respiratory depression ^b	1/17 (6%)	1/27 (4%)	0/22 (0%)
Pruritus ^c	5/17 (29%)	6/27 (22%)	5/22 (23%)
Nausea/vomiting ^c	5/17 (29%)	7/27 (27%)	4/22 (18%)
Urinary retention ^d	1/17 (6%)	0/27 (0%)	1/22 (4%)
Days of treatment with epidural morphine (mean $\pm$ SD)	3.3 $\pm$ 2.0	3.5 $\pm$ 1.9	3.9 $\pm$ 2.0

^aThere are no statistically significant differences in the incidence of any of the side effects among the three age groups (Fisher's exact test). There are no statistically significant differences in the duration of treatment among the three age groups (analysis of variance).

^bAny respiratory rate of 8 or less seen with hourly observations during the first 48 hr after surgery.

^cSymptom distressing enough to result in pharmacologic treatment.

^dThis population has indwelling bladder catheters after surgery. Urinary retention is defined as reinsertion of a bladder catheter after its initial removal.

ceptors in the dorsal horn of the spinal cord and a systemic effect that follows vascular uptake of drug from the epidural space. Advancing age increases the analgesic response to parenterally administered narcotics (5). The reduced dose requirements noted in our older patients might relate in part to a greater analgesic effect from systemically absorbed morphine.

Gustafsson et al. (1) measured CSF concentrations of morphine after epidural administration. In spite of large interpatient variability, older patients tended to have higher levels of CSF morphine than younger patients given the same epidural dose.

The relation between age and the effective doses of a number of local anesthetics is well established (6). Explanations include decreased effectiveness of neural barriers with age, decreased elimination of drug through intervertebral foramina resulting in higher CSF concentrations, and progressive decline in the nerve population of the neuraxis with age. These same factors may also apply when epidural morphine is used.

Figure 2 shows that we achieved excellent analgesia at rest in most patients. Coughing can produce severe pain in the immediate postoperative period and represents a useful bedside test of analgesia. Coughing in this population (Fig. 3) did not produce severe pain in most cases. In our judgment the reported pain levels in this population represent excellent postoperative analgesia.

The frequency with which side effects occurred did not change in relation to patient age. One patient each

in the <40 and 40-60 age groups demonstrated a respiratory rate of 8 breaths/min on one occasion. This technically fit our criteria for respiratory depression but we doubt that these isolated single observations are clinically significant. No other signs of respiratory depression were present in these patients and no treatment was required.

The period of time over which epidural morphine was administered tended to increase with age but this trend was not statistically significant. Treatment with epidural morphine was continued until return of bowel function and tolerance of a liquid diet permitted administration of an orally effective analgesic. It is possible that bowel function returns more slowly in older patients after abdominal hysterectomy.

In summary, we have shown that in women undergoing abdominal hysterectomy, age is a useful predictor of the dose of epidural morphine needed to control postoperative pain. Large interpatient varia-

bility requires careful adjustment of doses for individual patients in order to achieve optimal benefit and safety.

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Response of the Heart to Acute Hypertension during Halothane, Enflurane, and Isoflurane Anesthesia

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COETZEE A, FOURIE P, BADENHORST E. Response of the heart to acute hypertension during halothane, enflurane, and isoflurane anesthesia. *Anesth Analg* 1987;66:1219-26.

In the open chest dog model, the response of the left ventricle exposed to acute mechanical hypertension was evaluated while the animals were receiving various concentrations of halothane, enflurane, and isoflurane. Myocardial contractility was quantified by the end-systolic pressure-length relation (ESPL). When the mean aortic pressure was increased by 40% above the control value for a given concentration of inhalation agent, the end-diastolic volume increased and thereby maintained stroke work. However, as the end-tidal

concentrations of the anesthetics increased, this compensatory mechanism became progressively more ineffective as a result of myocardial depression caused by the anesthetics. No evidence could be found of an improvement in myocardial contractility as the aortic pressure was increased. Mild depression of myocardial contractility could be demonstrated for 1.1 MAC halothane, 0.6 MAC enflurane, and 1.0 MAC isoflurane. Severe depression of contractility occurred at 2.3 MAC halothane, 1.2 MAC enflurane, and 1.5 MAC isoflurane.

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane, isoflurane. BLOOD PRESSURE—hypertension. HEART—contractility.

When the afterload of the left ventricle (LV) is acutely increased, stroke volume (SV) decreases, an inverse relation that is more pronounced if myocardial depression is present (1). Compensatory mechanisms, such as an increase in heart rate (HR), the heterometric (Starling) (2), and homeometric autoregulation (Anrep effect) (3,4), will tend, however, to restore the SV toward normal and thereby maintain an effective circulation. The heterometric autoregulation is defined as the direct relation (within certain limits) between the end-diastolic ventricular volume and the subsequent stroke volume (diastolic reserve), whereas the homeometric autoregulation refers to an increase in myocardial contractility (systolic reserve) when the aortic pressure is increased.

In this study, we examined the response of the heart during acute increases in aortic pressure in dogs anesthetized with various concentrations of halo-

thane, enflurane, or isoflurane. We were especially interested in determining whether the heterometric or homeometric autoregulation (or both) operated under general anesthesia. To evaluate myocardial contractility, we applied the principles of the load and heart rate independent index; that is, the end-systolic pressure-volume (ESPV) relation (5-10), to the end-systolic pressure-length (ESPL) relation (11-13). The ESPL is not only useful for the determination of myocardial contractility, but can also be used to describe the pump function of the heart, because this ratio determines the amount of myocardial fiber shortening that can occur for a given end-diastolic volume (EDV) and contractile state (14).

Methods

Thirty mongrel dogs (mean weight 19.20 ± 3.6 kg [SE]) were used for this study. The dogs were cared for according to institutional and national guidelines for laboratory animals. Permission for the study was obtained from the Ethical Committee of the Faculty of Medicine, University of Stellenbosch.

Dogs were premedicated with intramuscular morphine 1.5 mg/kg and anesthesia was induced with fentanyl 15 μ g/kg and thiopental 15 mg/kg IV. They were intubated and ventilated with 40% oxygen and

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Work done for this publication is part of an MD thesis by Prof. Coetzee at the University of Stellenbosch. The supervisor is Prof. H. Weich, MMed, FACC, MD.

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60% nitrogen (rebreathing system with CO₂ absorber; fresh gas inflow, 3 L/min). Anesthetics were vaporized from a calibrated vaporizer (halothane, Drägerwerk, Germany; enflurane and isoflurane, Cyprane, UK) and the end-tidal gas concentration was monitored with an anesthetic gas monitor (Normac, Datex, Finland). Tidal volume was adjusted to maintain the PaCO₂ between 38 and 42 mm Hg.

Normal saline and 5 ml/kg and 7 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ fentanyl were infused into a front leg vein. The temperature of the operating table was controlled and blood temperature was maintained at 36.5 to 37.3°C as measured by the thermistor at the tip of the pulmonary artery catheter.

Through an incision in the neck, a 16-g arterial cannula was inserted through the carotid artery into the aorta (the tip being 1 cm from the aortic valve). This was connected to a pressure transducer (Statham P23; natural frequency 50.3 Hz) in order to measure arterial blood pressure. A 7F pulmonary artery catheter (Edwards Laboratory, USA) was inserted through the external jugular vein and positioned in the pulmonary artery. The position of the catheter was verified after the chest was opened and the pulmonary artery could be palpated. Cardiac output was calculated with a cardiac output computer (Mansfield 9530, USA) after manually injecting 5 ml 5% dextrose (0°C) in <4 sec into the proximal lumen of the catheter at the end of expiration. The mean of three values is reported in this study. After the experiments were completed, the atrium was opened to verify that the injectate port was in the right atrium.

Through the femoral artery and vein, size 8/14F occlusion catheters (Edwards Laboratory, USA), were placed in the aorta and inferior vena cava. The tip of the aortic catheter was 1 cm distal to the aortic arch in the descending aorta and the tip of the vena cava catheter was positioned between the diaphragm and right atrium. The catheters were used to change the preload and afterload of the heart to construct end-systolic pressure-length relations.

A left thoracotomy and pericardiotomy were performed and the heart was suspended in a pericardial cradle. An 18-g soft cannula was placed through a stab incision in the right ventricle outflow tract and positioned in the proximal pulmonary artery. A 16-g cannula was sutured into the apex of the LV and was connected to a Statham P23 Db pressure transducer with a natural frequency 50.6 Hz to measure LV pressure. Using a magnified calibration, left ventricle end-diastolic pressure (LVEDP) was obtained from the LV catheter.

Two piezo electric crystals (Schuessler and Associates, USA) were positioned 1 cm apart in the LV

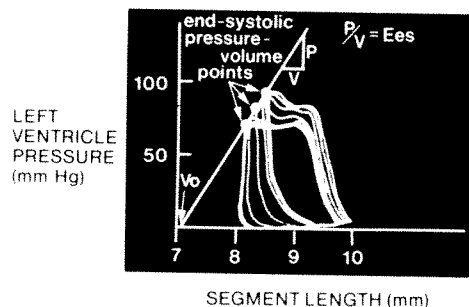


Figure 1. An example of the pressure-length loops generated in this study. The end-systolic pressure-length points are indicated and, because the end-systolic pressure-length ratio is a constant, the end-systolic pressure-length relation (ESPL or Ees) is linear. The ESPL (or Ees) is a sensitive and load-independent index of myocardial contractility. The intercept on the abscissa (V_0) is the volume in the ventricle when the LV pressure is zero. Because this study used regional length and not volume, V_0 represents the segmental length at the time the LV pressure is zero, hence the unit of measurement is the millimeter.

endocardium perpendicular to a line from the aortic root-apex of the heart, 1 cm from the left anterior descending (LAD) coronary artery, and halfway between the apex and aortic root. Endocardial fiber length was measured during the cardiac cycle (Ultrasonic Dimension System, Schuessler and Associates) and the maximal fiber length ($L_{\max}$) was taken at the time the sharp upslope of the LV pressure started (as were LVEDP) and the minimal length ($L_{\min}$) at the time of aortic valve closure. Systolic shortening ($dL = L_{\max} - L_{\min}$) could then be determined and was normalized for $L_{\max}$ and expressed as a percentage ($dL\%$). Left ventricular end-diastolic volume (LVEDV) was extrapolated from $L_{\max}$.

Data were recorded on a six-channel recorder (Beckman Instruments, Palo Alto, CA), all recordings being made 5 sec after the ventilator was disconnected (zero airway pressure). Calibrations were done with a mercury manometer before and during experiments.

The LV pressure signal and endocardial fiber shortening were combined on an oscilloscope (Tektronix Inc., Beaverton, OR model 5103N) to give a continuous pressure-length loop (11). Standard calibrations were used throughout. The pressure length loops obtained were used to identify the ESPL point (Fig. 1). By decreasing the volume of the heart (inferior vena cava balloon inflated), various ESPL points could be obtained. These were used to construct the end-systolic pressure-length line that is linear and is a load-independent index of myocardial contractility (5-10). From this line, the intercept on the abscissa (length) could be calculated, a point referred to as V_0 and with units in millimeters. At the time LV pressure is zero, V_0 refers to the regional myocardial length.

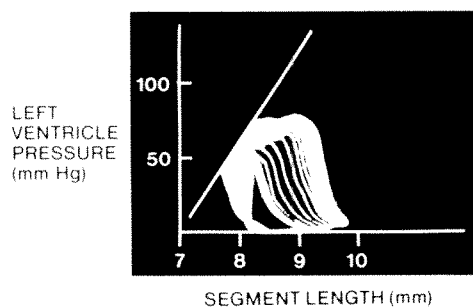


Figure 2. The response of the pressure-length loop when the LV preload decreased. The linear character of the ESPL is demonstrated in this recording.

From the RR interval of the ECG, HR was recorded; dp/dt_{max} was obtained from the LV pressure recordings. Aortic and pulmonary artery (mixed venous) blood was anaerobically withdrawn in chilled preheparinized syringes that were kept under ice until the samples were analyzed for blood gas tensions (IL 282 Co-oximeter, IL 613 Blood Gas Analyzer; Instrumentation Laboratories, Inc., Lexington, MA). Hemoglobin and carboxyhemoglobin levels, as well as hemoglobin saturation, were determined.

Differences between the ESPL during hypertension and under normotensive conditions were evaluated with the Wilcoxon-rank sum test. Analysis of variance for repeated observations (MANOVA) was used to compare cardiovascular data. The initial value (control), i.e., the lowest concentration for each anesthetic, was compared with each subsequent value for that particular parameter. The paired *t*-test was used to compare the hemodynamic data between normotension and hypertension. A value of $P < 0.05$ was accepted as being statistically significant.

Experimental Design

After completion of surgery, calibrations were performed, arterial blood gas tensions checked, and 20–25 min were allowed for equilibration at the lowest anesthetic gas value used in the experiments. Each group comprised ten dogs and end-expiratory anesthetic concentrations used were:

- Halothane (%): 0.5, 0.7, 1.0, 1.5, and 2.
- Enflurane (%): 0.8, 1.2, 1.7, 2.1, and 2.6.
- Isoflurane (%): 0.7, 1.1, 1.5, 1.9, and 2.1.

No effort was made to have equal concentrations of anesthetics but, when indicated, comparisons were made in terms of MAC values. MAC was accepted as 0.86% for halothane, 2.2% for enflurane, and 1.46% for isoflurane (15).

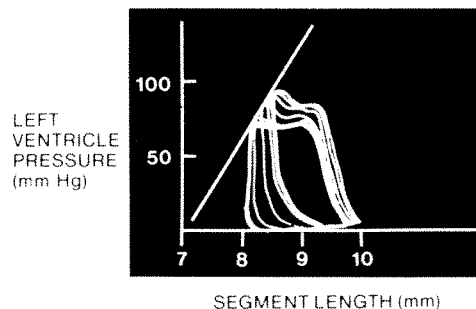


Figure 3. The ESPL as recorded after a 300-sec period of hypertension. As the aorta balloon was deflated, the change in the pressure-length loop was registered and from the end-systolic pressure and length points, the ESPL could be constructed.

Twenty-five minutes were allowed for equilibration between each step and, during that period, calibrations, arterial blood gas tensions, and pH were measured and ventilation was corrected as required.

After recording hemodynamic data, the inferior vena cava balloon was inflated over a 5-sec period and the resulting change in the pressure-length loop was photographed (Fig. 2). From this photograph the ESPL for the normotensive phase was calculated. Thereafter the balloon was deflated and the aortic balloon was inflated to increase aortic pressure. The proximal aortic hypertension was maintained for 5 min before the hemodynamic data were again recorded. The aortic balloon was then deflated and the change in the pressure-length loop after deflation was used to construct the ESPL relation for the hypertensive phase (Fig. 3).

Results

Table 1 shows the ESPL relation (as an index of myocardial contractility) and V_0 . No statistically significant difference could be demonstrated when the values obtained during normotension (N) were compared with hypertensive (H) values obtained for the various concentrations of anesthetics. Myocardial contractility (ESPL) did not change when hypertension was induced, and a parallel shift in the ESPL ratio could not be demonstrated (constant value for V_0).

Table 2 shows the hemodynamic data. As the concentration of halothane was increased, HR remained constant, but the MAP increased significantly during induction of hypertension. When $\geq 1\%$ halothane was administered, the MAP attained during hypertension was significantly less than the MAP during hypertension with 0.5% halothane. Although the LVEDP increased significantly once hypertension was induced with each concentration of halothane, the various hypertensive values did not differ significantly

Table 1. Normotensive (N) and Hypertensive (H) Values for ESPL (End-Systolic Pressure-Length Relation) and V_0 (the volume of the LV at the time LV pressure is zero).

Normotension		Hypertension	
ESPL (mm Hg/mm)	V_0 (mm)	ESPL (mm Hg/mm)	V_0 (mm)
36.9	4.6	49.5	3.8
108.0	4.6	109.0	4.6
88.0	4.7	74.0	4.4
51.0	4.4	51.0	4.5
37.0	7.0	41.0	7.3
21.0	6.1	16.0	4.9
84.0	7.1	84.0	7.1
52.0	7.3	52.0	7.3
44.0	7.8	50.0	8.5
55.0	7.7	43.0	7.4
55.0	4.0	34.0	7.9
29.0	8.6	30.0	7.9
44.0	7.4	35.0	6.7
18.0	8.2	17.0	8.4
17.0	7.9	21.0	8.9
84.0	6.6	68.0	6.3
69.0	6.5	47.0	6.1
58.0	6.5	64.0	7.1
43.0	6.3	38.0	6.1
38.0	6.5	40.0	6.5
95.0	8.6	75.0	8.3
89.0	8.7	72.0	8.7
47.0	8.2	50.0	8.2
35.0	8.1	38.0	8.3
35.0	8.6	35.0	8.6
103.0	7.2	100.0	7.3
86.0	7.1	72.0	7.0
56.0	5.4	54.0	7.2
50.0	7.2	39.0	6.7
33.0	7.3	32.0	6.9
17.0	4.7	17.0	4.7
147.0	8.6	116.0	8.5
94.0	8.4	97.0	8.5
93.0	8.6	51.0	7.9
47.0	7.9	47.0	8.1
40.0	7.8	42.0	8.1
36.0	7.8	35.0	7.1
27.0	7.6	45.6	8.3
24.0	7.2	36.8	7.9
25.1	7.4	30.0	7.8
26.0	8.7	34.0	8.4
26.3	8.6	34.0	8.5

In this study regional length is used as an index of volume and V_0 therefore is in millimeters. Values shown ($n = 42$) are those in which successful ESPL measurements could be made during hypertension, and include data for all three anesthetic agents at various concentrations.

from the initial hypertensive value. $L_{\max}$ is used as an index of end-diastolic volume, and a significant increase was demonstrated during hypertension for each level of anesthetic concentration tested. Left ventricular stroke work index (LVSWI) increased during H for each of the concentrations of halothane, but when 2% halothane was administered, the LVSWI during hypertension was significantly less than that measured during hypertension at 0.5% halothane.

During the enflurane study, HR remained constant throughout the normotensive and hypertensive periods. Again there was a significant increase in MAP when the aortic balloon was inflated, and this resulted in a statistically significant increase in both LVEDP and $L_{\max}$ during hypertension for each concentration of enflurane examined. The LVEDP during hypertension was significantly greater at 1.7% enflurane when compared with 0.8% enflurane. A similar observation was made for 2.1 and 2.6% enflurane when compared with 0.8% enflurane. There was a statistically significant increase in LVSWI during hypertension with each of the concentrations of enflurane examined. At 2.1 and 2.6% enflurane, LVSWI measured during hypertension were less than the hypertensive values obtained during 0.8% enflurane.

In the isoflurane study, there was a significant decrease in HR during hypertension when compared with the normotensive value. However, this did not occur during the administration of 2.1% isoflurane. Mean arterial pressure increased significantly when the intra-aortic balloon was inflated for each of the concentrations of isoflurane examined. This resulted in a statistically significant increase in LVEDP during hypertension at all the levels of isoflurane, and the LVEDP values measured during hypertension at 1.9 and 2.1% were significantly greater than the values obtained at 0.7% isoflurane. $L_{\max}$ increased significantly at 1.1% isoflurane and all subsequent concentrations during hypertension. At the highest concentration of isoflurane, $L_{\max}$ was significantly greater during hypertension than the value that was measured during administration of 0.7% isoflurane. Again the LVSWI increased significantly during hypertension with all the concentrations of isoflurane. At 1.52% and all subsequent concentrations of isoflurane, LVSWI levels during hypertension were significantly less than the values obtained at 0.7%.

In Figure 4 the results are demonstrated. For each anesthetic agent, a Starling plot was attempted to demonstrate the relation LVEDP and LVSWI. In these graphs, various response options are indicated, and it can be shown that halothane caused mild myocardial depression at 1.1 MAC. Severe depression occurred at 2.3 MAC. Enflurane caused mild myocardial depression at 0.6 MAC and severe depression at 1.2 MAC. Isoflurane administration of 1.1 MAC resulted in mild myocardial depression, and at 1.5 MAC severe myocardial depression was evident.

Discussion

Previous studies have demonstrated that halothane, enflurane, and isoflurane depress myocardial contractility (16-18). Given the inverse relation between

Table 2. The Response of the Myocardium to an Acute Increase in Left Ventricular Afterload for 30 Dogs

Halothane (%)	0.5		0.7		1.0		1.5		2.0	
	N	H	N	H	N	H	N	H	N	H
HR	94.70	86.40	95.80	88.80	93.70	86.00	98.50	97.50	97.50	101.20
(beats/min)	± 5.82	± 5.82	± 3.99	± 5.49	± 4.20	± 4.85	± 3.40	± 4.30	± 3.80	± 5.60
MAP	77.73 ^d	106.73	75.93 ^d	104.93	71.33 ^d	99.27 ^c	57.13	95.33 ^c	42.40 ^d	74.33 ^d
(mm Hg)	± 4.58	± 4.78	± 4.40	± 4.59	± 3.41	± 3.60	± 2.69	± 6.04	± 2.28	± 5.23
LVEDP	5.70 ^b	8.55	6.21 ^b	8.20	6.35 ^b	8.74	5.60 ^b	9.50	5.85 ^d	10.00
(mm Hg)	± 0.75	± 1.13	± 0.65	± 1.30	± 0.65	± 0.83	± 0.84	± 1.10	± 0.86	± 0.95
L _{max}	10.73 ^b	11.26	10.78 ^b	11.21	10.69 ^d	11.21	10.86 ^d	11.34	10.86 ^d	11.44
(mm)	± 0.93	± 1.02	± 0.91	± 0.96	± 0.91	± 0.97	± 0.93	± 0.93	± 0.93	± 0.96
LVS WI	34.98 ^d	43.47	32.55 ^c	38.64	24.82 ^a	31.96	14.52 ^d	21.18	7.49 ^d	10.58 ^s
(gm·m/m ²)	± 5.02	± 5.41	± 5.00	± 5.91	± 2.69	± 4.55	± 1.20	± 1.87	± 0.84	± 1.29
Enflurane (%)	0.8		1.2		1.7		2.1		2.6	
	N	H	N	H	N	H	N	H	N	H
HR	96.00	87.00	100.00	93.00	99.00	95.00	99.00	94.20	102.50	103.20
(beats/min)	± 9.04	± 7.03	± 5.92	± 6.95	± 7.52	± 7.01	± 7.40	± 7.50	± 6.91	± 5.50
MAP	69.36 ^d	101.10	70.40 ^d	109.92	66.20 ^d	105.40	58.40 ^d	94.90	51.03 ^d	87.93
(mm Hg)	± 4.64	± 7.81	± 2.58	± 5.24	± 2.47	± 5.24	± 2.40	± 4.70	± 2.75	± 4.04
LVEDP	5.40 ^b	7.10	6.04 ^b	8.68 ^d	6.15 ^b	8.98 ^c	5.44 ^d	9.30 ^c	6.00 ^d	10.60 ^s
(mm Hg)	± 0.37	± 0.34	± 0.68	± 0.52	± 0.54	± 0.68	± 0.70	± 0.70	± 0.50	± 0.63
L _{max}	12.13 ^d	12.61	12.07 ^d	12.89 ^c	12.21 ^d	12.91 ^d	12.25 ^d	13.02 ^s	12.30 ^d	13.18 ^s
(mm)	± 0.95	± 0.93	± 0.98	± 0.98	± 0.92	± 0.99	± 0.95	± 0.98	± 0.97	± 0.92
LVS WI	26.99 ^b	35.24	22.25 ^b	33.03	20.61 ^d	28.86 ^c	15.31	22.47 ^s	10.56 ^d	15.14 ^s
(gm·m/m ²)	± 3.19	± 2.26	± 3.29	± 3.35	± 2.00	± 2.87	± 1.51	± 3.56	± 1.00	± 1.37
Isoflurane (%)	0.7		1.1		1.5		1.9		2.1	
	N	H	N	H	N	H	N	H	N	H
HR	114.00 ^b	98.90	114.60 ^b	90.90	120.50 ^a	97.60	126.30 ^b	108.20	125.10	122.10
(beats/min)	± 6.22	± 6.86	± 6.34	± 6.72	± 5.57	± 6.15	± 4.32	± 4.86	± 4.24	± 6.07
MAP	84.30 ^d	112.03	79.40 ^d	113.63	57.00 ^d	114.87	66.07 ^d	104.73	60.73 ^d	100.67
(mm Hg)	± 7.43	± 6.28	± 5.28	± 5.83	± 3.65	± 5.58	± 4.11	± 5.63	± 4.29	± 7.90
LVEDP	6.01 ^b	7.65	5.80 ^c	8.13	6.20 ^c	9.99	5.39 ^b	11.68 ^d	7.02 ^d	12.73 ^d
(mm Hg)	± 1.00	± 1.28	± 1.12	± 1.10	± 0.83	± 1.60	± 0.96	± 1.20	± 1.59	± 1.93
L _{max}	10.62	10.96	10.55 ^d	11.24	10.55 ^d	11.16	10.72 ^b	11.18	10.90 ^d	11.63 ^s
(mm)	± 0.48	± 0.52	± 0.48	± 0.50	± 0.51	± 0.45	± 0.47	± 0.39	± 0.45	± 0.52
LVS WI	27.27 ^b	36.16	24.21 ^d	32.62	21.19 ^d	30.88 ^c	16.09 ^b	21.64 ^d	12.56	16.09 ^s
(gm·m/m ²)	± 3.29	± 4.20	± 2.50	± 3.02	± 2.14	± 3.28	± 2.00	± 2.82	± 1.61	± 2.56

n = 10 for each anesthetic agent. N, normotension; H, hypertension. Statistical analysis done between H and N values (footnotes marked ^a, ^b, ^c, and ^d) and between the initial H value and the subsequent H values (footnotes marked ^e, ^f, and ^g).

^a, ^e P < 0.05.

^b, ^f P < 0.01.

^c P < 0.005.

^d, ^g P < 0.001.

LV ejection pressure and stroke volume (1), it can be predicted that in the presence of the inhalation anesthetics, the circulation will become compromised if acute hypertension is induced. This concept was verified for halothane by Merin et al. (16) and Gersh et al. (19). Merin et al. (18) demonstrated an increase in the LVEDP during hypertension, and although the diastolic reserve mechanism was invoked, SV still decreased. No increase in contractility (dp/dt_{max}) could be demonstrated during the increase in aortic pressure. However, the rate of rise in LV pressure as an index of myocardial contractility is influenced by the loading conditions of the heart, heart rate, and con-

duction (20,21), and therefore the effect of acute hypertension on myocardial contractility, in the presence of inhalation anesthetics, still requires verification. Furthermore, the response of the heart as a pump in the presence of halothane, enflurane, and isoflurane needs to be elucidated during acute hypertension. This study endeavors to examine the effect of acute mechanical hypertension on myocardial function in the presence of halothane, enflurane, and isoflurane, with special reference to the available compensatory options, i.e., an increase in HR or the utilization of the systolic or diastolic reserve mechanisms.

In this study, we found that the heart used the

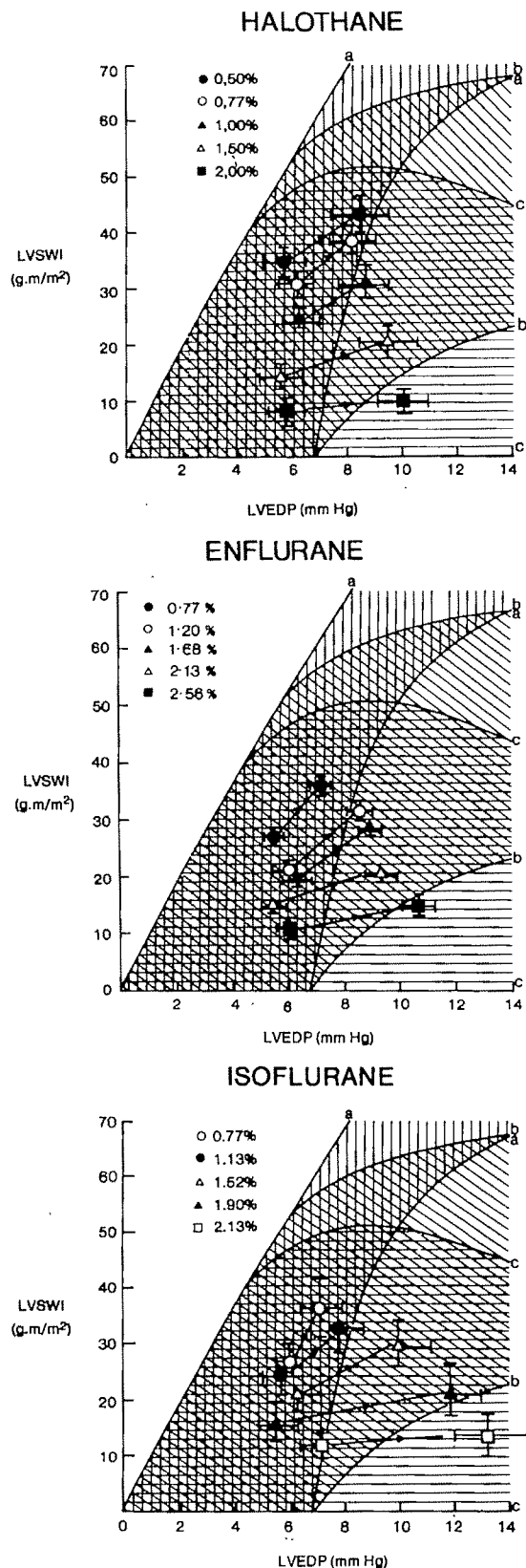


Figure 4. The response of the LV as the afterload was acutely increased with an aortic balloon. At the lower concentrations of the anesthetics, left ventricular stroke work index (LVSWI) and LVEDP increased. As the concentration of anesthetics were increased, the LVSWI increased less when hypertension was induced; however, LVEDP still increased significantly. This observation supports the concept that halothane, enflurane, and isoflurane depress myocardial contractility. The response areas (see Fig. 4) were taken from the study of Ross and Braunwald (23) in humans. However, the principle of using these clinically applicable variables to demonstrate progressive myocardial depression caused by the anesthetic agents is still valid. The area a-a indicates a normal response; b-b is the response of the mildly depressed heart and c-c represents severe myocardial depression.

values for the anesthetics, a substantial increase in LVSWI could be demonstrated during acute hypertension. However, as the concentration of the anesthetic agents increased, the increase in LVSWI became less pronounced. This suggests that the diastolic reserve mechanism became less efficient at the higher concentrations of the anesthetics, a finding indicative of a progressive depression of myocardial contractility as the anesthetic depth was increased (Fig. 4). To illustrate this concept, we compared the studies on humans by Ross and Braunwald (22) with the results obtained in our study. Ross and Braunwald used an infusion of angiotensin to increase arterial pressure; by doing so, they could classify myocardial function as either normal, mildly depressed, or severely depressed with reference to response of the LVSWI and LVEDP. In normal hearts, the increase in pressure was associated with an increase in LVSWI and a slight increase in LVEDP. In the mildly depressed heart, LVEDP increased significantly after the elevation of blood pressure and LVSWI was maintained at control values or demonstrated a slight increase. In the severely depressed heart, LVEDP increased substantially and LVSWI decreased. If these concepts are extrapolated to this study, it can be demonstrated that mild myocardial depression occurred at 1.1 MAC halothane, 0.6 MAC enflurane, and 1.0 MAC isoflurane. Severe depression occurred at 2.3 MAC halothane, 1.2 MAC enflurane, and 1.45 MAC isoflurane.

It appears that halothane causes less depression than does isoflurane; the latter is also less depressing than enflurane. There are, however, problems in using Ross and Braunwald's (22) results and applying them to our study in open chest dogs. Given the fact that stroke volume is less in dogs, it is expected that LVSW will be less in the dog than in humans. To overcome this problem, we normalized the data for body surface area and assume a correlation exists between the normalized human and dog values. Furthermore, only certain concentrations of the anesthetic agents were evaluated and, although it appears that a graded response exists between the concentra-

heterometric mechanism extensively (or diastolic reserve, Starling curve of the heart) in an effort to maintain LVSWI during acute hypertension. At the lower

tions examined in this study, the authors cannot discuss the response of the heart other than at these particular values. The values at which mild and severe depression occurred should therefore be viewed with this in mind. Nevertheless, Figure 4 is a useful method of demonstrating how the heterometric autoregulation became less effective in maintaining LVSWI as the myocardium was depressed by the anesthetics.

With halothane and enflurane, HR did not change when the proximal aortic pressure was increased. With isoflurane, the rate decreased during hypertension, except at the higher concentrations administered. Acute hypertension in the course of general anesthesia is often due to a sympathoadrenal response when the anesthetic depth is insufficient. Under these circumstances, the increase in HR is accompanied by an increase in blood pressure. However, the catecholamines responsible for the rate and pressure response to noxious stimuli will also increase myocardial contractility and thereby enable the LV to deliver a constant SV against a higher afterload. Our model therefore cannot be applied to these circumstances and should rather be used to predict the response of the heart to mechanical hypertension, such as the application of an aortic cross-clamp or partial occlusion of the proximal aorta with a side-clamp during insertion of an aorta perfusion cannula. The HR was not used as a reserve mechanism in the dogs given halothane, enflurane, or isoflurane. With isoflurane there was a significant decrease in HR that was probably a result of the baroreceptor response association with the acute rise in blood pressure.

To enable us to study the systolic reserve mechanism of the heart, we used the LV pressure-length loop. It must be emphasized that the index of contractility used in this study, i.e., the ESPL relation, refers to regional myocardial function as opposed to global myocardial function, which can be quantified with the ESPV relation (11-13). Because the ESPL ratio of the LV is a constant, it can be described by simple linear regression mathematics (Fig. 1) (5,10). The ESPL relation and the pressure-length loop is advantageous in that it can quantify myocardial contractility (ESPL ratio) but can also be used to describe the function of the heart as a pump, because the ESPL relation is the limiting factor to myocardial shortening during ejection (14). Therefore, if end-diastolic volume, the end-systolic pressure, and ESPL ratio are known, stroke volume can be predicted (Fig. 1).

In this study, no evidence of an increase in myocardial contractility (systolic reserve, Anrep effect, or homeometric autoregulation) could be demonstrated during hypertension. The ESPL ratio and V_0 during hypertension remained similar to values obtained during normotension and the absence of a nonparallel

shift in the ESPL ratio is sufficient evidence to prove that myocardial contractility did not change during the acute increase in MAP. Therefore, we were unable to confirm the presence of the homeometric autoregulation mechanism in the dog heart given halothane, enflurane, and isoflurane. However, the concept of a homeometric autoregulatory mechanism, described by Von Anrep (3) and discussed in subsequent studies by Sarnoff et al. (4), fails to convince us that such a mechanism exists. Studies by Monroe et al. (23) using an isovolemic heart model indicated that temporary myocardial ischemia can explain the observation made by Von Anrep and Sarnoff. The explanation put forward by Monroe et al. (23) suggests that the heart is marginally ischemic, an assumption not applicable to the ejecting heart (24). The observations made by Von Anrep (3) can be explained by a steep slope for the pressure-volume relation (i.e., excellent contractility), because it would be possible for the heart to maintain its SV by a small increase in end-diastolic volume when the MAP is increased. Contrary to the studies of Von Anrep (3) and Monroe et al. (23), Van den Bos et al. (25) found a decrease in dp/dt_{max} when LV afterload was increased. However, given the load-dependent character of this index, the meaning of this observation is uncertain.

We conclude that during halothane, enflurane, or isoflurane anesthesia the heart depends mainly on diastolic volume augmentation to maintain stroke volume when left ventricular ejection pressure is increased. However, despite this mechanism, LVSWI did not improve to the same extent at the higher concentrations of the anesthetic agents when compared with the initial low concentration used for control purposes. This supports the theory that halothane, enflurane, and isoflurane depress myocardial contractility in a dose-dependent manner. Limitation to the use of the diastolic reserve, e.g., low intervacular volume, restrictive myocardial, or pericardial pathology, will probably accentuate the decrease in SV once LV ejection pressure is acutely increased. This will be especially applicable at the higher concentrations of the anesthetics. Finally, although we examined the possibility that the homeometric autoregulatory mechanism exists, we could not confirm its presence in the anesthetized dog.

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Studies of the Toxicity of I-653, Halothane, and Isoflurane in Enzyme-Induced, Hypoxic Rats

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in enzyme-induced, hypoxic rats. *Anesth Analg* 1987;66:
1227-9.

The physical stability and low blood solubility of the new inhaled anesthetic, I-653, imply that this agent produces limited or no toxic effects. To test this possibility, its effects were compared with those of other volatile agents on hepatic, renal, and pulmonary specimens taken from enzyme-induced, hypoxic rats. Male Sprague-Dawley rats were pre-treated with phenobarbital and exposed for 1 hr to 12% O₂ and no anesthesia (control) or to 1.2 MAC of one of three anesthetics: I-653, isoflurane, or halothane. Liver, kidney, and lung specimens were taken 24 hr after exposure con-

cluded. The livers of all rats given halothane (n = 6) had swelling (20.5 ± 5.7% of a lobule [mean ± SD]) and centrilobular necrosis (6.7 ± 2.1% of a lobule). Isoflurane produced only slight injury (6.7 ± 3.5% swelling and 1.0 ± 0.0% necrosis in 3 of 15 rats). No hepatic injury occurred in control rats (n = 20) or in those given I-653 (n = 16). Pulmonary and renal injury were not evident with any agent. Results suggest that I-653 has equivalent or less effect on hepatic, renal, and pulmonary integrity than currently available inhaled anesthetics.

Key Words: ANESTHETICS, VOLATILE—halothane, I-653, isoflurane. TOXICITY—halothane, I-653, isoflurane. LIVER—hepatotoxicity. KIDNEY—nephrotoxicity.

The new volatile anesthetic, I-653 (CF₂H-O-CFH-CF₃), has an appreciably lower blood/gas partition coefficient (0.42) than that for isoflurane (coefficient 1.4) or halothane (coefficient 2.5) (1-3). This lower solubility should decrease the time I-653 is retained in the body and thereby minimize its potential for toxic effects. I-653 is also more resistant to physical degradation than either halothane or isoflurane, suggesting that I-653 may have a greater resistance to biodegradation and toxicity (4). To test this hypothesis, we compared the effects of I-653, isoflurane, and halothane on the liver, kidney, and lung of hypoxic, enzyme-induced rats.

Materials and Methods

With the approval of the University of California, San Francisco Committee on Animal Research, we studied specific-pathogen-free, 2.5- to 3-month-old, male

Sprague-Dawley rats (Charles River Laboratories) weighing 250-350 g. Each rat was housed individually and had continuous access to standard rat chow before and after the study. Phenobarbital 1 mg/ml was added to the drinking water for 5 days. We discarded rats that drank less than 10 ml/day. On the sixth day, plain tap water was provided.

Twenty-four hours after withdrawal of phenobarbital, four rats were placed in a four-cylinder test apparatus we have described elsewhere (5). The dimensions of each cylinder (length, 27 cm; internal diameter, 6.25 cm) permitted the entrance of a single rat but prevented its turning around once within the chamber. Our limited supply of I-653 required the use of a closed anesthetic system (5). Although specifically needed for the test of the I-653 (because of the limited supplies of I-653), a closed system was applied with all anesthetics. The ends of each chamber were sealed with rubber stoppers. Each stopper had a pass-through, one in the front (at the rat's head) for sampling gases and one at the rear for a rectal temperature probe. Each also had a pass-through for the delivery and exchange of gases. The sampling and injection ports were sealed with stopcocks when not in use.

Once the rats had entered the chambers, the rectal probes were inserted and secured with paper tape.

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The chambers were then sealed, and nitrogen was gradually introduced to decrease the inspired oxygen concentration to 11–13%, as measured with a Beckman E2 oxygen analyzer. Once hypoxic, the four rats were exposed to 1.2 MAC I-653, isoflurane, or halothane, or no anesthetic (control). MAC was assumed to be 5.7% for I-653, 1.4% for isoflurane, and 1.1% for halothane (6,7). Hypoxia was maintained for the 1-hr duration of exposure to the anesthetic. Control rats were also made hypoxic for this duration. Rectal temperatures were monitored throughout testing and were maintained between 37.5 and 38.5°C by applying heat (infrared lamps) or cold (ice) to the exterior of individual chambers. Carbon dioxide concentrations were measured with infrared analysis with a Beckman LB-2 analyzer and usually varied between 0.7 and 1.2%. The highest concentration measured was 1.65%. A total of 20 rats served as controls, 16 were given I-653, 16 were given isoflurane, and 8 were given halothane.

Anesthetic was introduced in an amount calculated to produce a rapid rise to 1.2 MAC. We determined the concentrations actually achieved from gas samples obtained sequentially from each chamber, usually at 5- to 10-min intervals. All samples were analyzed for anesthetic concentrations by gas chromatography. We used a Gow Mac model 750 gas chromatograph equipped with a 30-m-long, fused silica open tubular capillary column (internal diameter, 0.53 mm) coated with a 5- μ m-thick layer of methylsilicone oil (J & W Scientific DB-1). A nitrogen carrier stream of 6 ml/min was directed through the column with a "makeup" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop. The chromatograph was calibrated with secondary tank standards that had been calibrated with primary standards produced by injection of a liquid aliquot of anesthetic into a flask of known volume. However, the concentrations of I-653 required for anesthesia exceeded the linear range of our gas chromatograph. To reduce these concentrations into the linear range, we diluted each I-653 sample by a factor of 10, incorporating this dilution into the calculation of concentration.

At the end of the test period (1 hr), the reservoir bag was removed from the system and oxygen flushed through the system for a few seconds before removal of the rats from their chambers. The temperature probes were left in place while heat was applied to maintain rectal temperature above 37°C until the rats awoke (they invariably cooled slightly on removal from the

tubes). Control rats were treated identically to the anesthetized rats except that no anesthetic was given. That is, control rats were placed in the chambers, rectal probes were inserted and temperature controlled, and hypoxia was imposed for slightly more than 1 hr.

After awakening, the rats were returned to their individual cages and given standard rat chow and tap water, ad libitum. Twenty-four hours after anesthesia, the rats were killed by administration of 100% carbon dioxide. Specimens of liver, kidney, and lung were obtained and placed in 10% buffered formalin. For each specimen, a slide was prepared and coded, and all slides for a given tissue were arranged in a random array. A pathologist (LDF), who was not informed of the specific treatment for each rat, graded all specimens for the presence or absence of injury. Hepatic specimens were also graded for the percentage of the lobule that showed swelling and for the percentage that showed necrosis. The sum of these two grades of injury was considered the total percentage of lobular injury. Pulmonary specimens were graded for acute and chronic injury and the presence of pneumonia and atelectasis.

Analysis of variance, Fisher's exact test, or χ^2 analysis were applied. We accepted a *P* value of <0.01 as statistically significant.

Results

All control rats and all rats given I-653 survived testing. Two rats given halothane and one given isoflurane died, apparently of partial obstruction to ventilation during testing. The average concentration of oxygen and the MAC administered did not differ significantly among groups according to analysis of variance (Table 1).

The groups did differ in the extent of hepatic injury. Halothane caused a greater degree and a greater incidence of injury than the other two anesthetics (Table 1). Isoflurane produced mild hepatic injury in 3 of 15 rats, but neither the degree nor incidence of injury was significantly different from that observed in control rats. Neither I-653 nor isoflurane produced significant increases in the incidence or degree of hepatic injury over the incidence or degree of injury in control rats. (Fisher's exact test for the difference in the incidence of hepatic injury in isoflurane-treated and control rats gave *P* = 0.11). Indeed, I-653 caused no hepatic injury, the same outcome observed in control rats.

The lung specimens from all groups displayed a similar degree of atelectasis, probably as a result of

Table 1. A Comparison of Hepatic Injury after Anesthesia in Enzyme-Induced, Hypoxic Rats

	Control (n = 20)	I-653 (n = 16)	Isoflurane (n = 15)	Halothane (n = 6)
% Oxygen	11.9 ± 0.2	11.5 ± 0.3	12.2 ± 0.6	12.2 ± 0.6
% of 1.2 MAC		95 ± 7	102 ± 4	91 ± 8
% of rats with hepatic injury	0	0	20	100
For injured hepatic lobules				
% of lobule injured	0	0	7.7 ± 3.5	27.2 ± 5.8
% of lobule necrosed	0	0	1.0 ± 0.0	6.7 ± 2.1

pulmonary collapse after death. However, no evidence of pneumonia or other pulmonary injury was apparent. Renal injury was not observed in any specimen.

Discussion

Our results suggest that I-653 is relatively free of hepatotoxic, pneumotoxic, or nephrotoxic effects in enzyme-induced, hypoxic rats. The hepatotoxic effects of halothane are consistent with our perception of the role of molecular instability in the production of hepatic injury in the enzyme-induced, hypoxic model. The order of instability of these anesthetics in the presence of soda lime is halothane > isoflurane > I-653 (4). The relationship of physical stability to stability in vivo for I-653 remains to be studied, and clinical studies of this promising new agent must confirm the safety suggested by the results of the present

experiment. If the present results apply to clinical practice, I-653 would appear to be as safe or safer than presently available anesthetics.

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Comparison of the Toxicity of I-653 and Isoflurane in Rats: A Test of the Effect of Repeated Anesthesia and Use of Dry Soda Lime

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EGER EI II, JOHNSON BH, FERRELL LD. Comparison of the toxicity of I-653 and isoflurane in rats: a test of the effect of repeated anesthesia and use of dry soda lime. *Anesth Analg* 1987;66:1230-3.

The low solubility and high stability of the new volatile anesthetic, I-653, suggest that this agent should have little or no toxic effect. This hypothesis was tested using repeated exposures to I-653, to isoflurane, or to no anesthetic. For 2 consecutive weeks, groups of 16 rats each were subjected

to a total of six 2-hr exposures to 100% oxygen and 1.6 MAC I-653, isoflurane, or no anesthetic. Twenty-four hours after the last exposure, the rats were killed by administration of 100% carbon dioxide and then autopsied. Specimens were taken from brain, pituitary, lung, heart, duodenum, pancreas, kidney, and liver. No tissue damage attributable to either anesthetic was found nor was weight gain affected.

Key Words: ANESTHETICS, VOLATILE—I-653, isoflurane.

The vulnerability of tissues to anesthetic-induced toxicity depends on many factors, including anesthetic solubility and stability. I-653 is a new, volatile anesthetic that has a blood/gas partition coefficient (0.42) appreciably lower than those for isoflurane (1.4), halothane (2.5), or the experimental anesthetic, sevoflurane (0.69) (1-4). This lower solubility should shorten the sojourn of I-653 in the body after anesthesia and thus reduce the likelihood of toxicity due to anesthetic degradation over time. Recovery from anesthesia is more rapid with I-653 than with sevoflurane, isoflurane, or halothane (5).

I-653 also resists degradation by moist soda lime (15% water) at increased temperatures, whereas all other potent inhalation anesthetics undergo some breakdown (6). However, in the presence of dry soda lime, I-653 slowly degrades. A breakdown product, probably fluoroform (CF_3H) (Dr. Vincent S. Venturilla, personal communication), appears in the chromatogram of I-653 exposed to dry soda lime (unpublished data). Dry soda lime is also more effective in degrading other volatile anesthetics such as isoflurane.

These data indicate that I-653 should have little or

no toxic effect. Consistent with this reasoning, we found that a single exposure to I-653 in enzyme-induced, hypoxic rats does not injure the liver, kidney, or lung (7). In the present study, we have tested the relative toxicities of I-653 and isoflurane in rats repeatedly anesthetized with these agents in the presence of dry soda lime.

Methods

With approval from the University of California, San Francisco Committee on Animal Research, we studied 48 specific-pathogen-free, 2.5-month-old, male Sprague-Dawley rats weighing 250-300 g (Charles River Laboratories). Housed individually in hanging, wire-mesh cages, all rats had continuous access to standard rat chow and tap water, except during the periods of study. Each rat was given an identification number, and his cage was so labeled. Sixteen rats were assigned to each of three groups: exposure to no anesthetic (control), to I-653, or to isoflurane.

Two factors dictated the use of a closed anesthetic system for our studies of I-653. First, I-653 is expensive to manufacture, and the MAC of I-653 is 5.7% (8), suggesting that it is likely to be expensive to use in a clinical setting. The use of a closed anesthetic system would therefore be prudent for economic reasons. Second, any toxic effect borne of I-653 interaction with soda lime would be most evident after exposure in a closed circuit. For consistency, a closed circuit was also used for our studies of the isoflurane and control groups.

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The circuit has been described previously (5) and mimics a circle absorption system. The absorber was charged for each study with fresh, dry soda lime. The gas stream issuing from the absorber was divided into eight streams, each of which was directed into an individual chamber housing a single rat. Each chamber had two additional pass-throughs, one in the front (at the rat's head) for sampling gases and one at the rear for placement of a rectal temperature probe. The sampling and injection ports were sealed with stopcocks when not in use. The Plexiglas chambers were 27 cm long and 6.25 cm in internal diameter. These dimensions permitted a single rat to enter a chamber, but prevented its turning around once within.

After each of eight rats was weighed and had entered a chamber, a rectal probe was placed and secured to the tail with paper tape. All eight rats were then exposed to a high flow rate of oxygen (in excess of 6 L/min) for 5 to 10 min to produce denitrogenation. The reservoir bag was removed from the anesthetic circuit during this period of flushing. The system was then sealed, except for the opening to the oxygen bypass.

Anesthetic was then introduced in an amount calculated to produce a rapid increase to 1.6 times MAC. We chose 1.6 MAC because preliminary studies indicated that this was the highest concentration that could be administered for a 2-hr period without producing undue depression of ventilation. Control rats were given no anesthetic. We assumed MAC for I-653 to be 5.7%, and MAC for isoflurane to be 1.4% (8,9). The concentrations actually achieved were determined from gas samples obtained from the chambers in sequence, usually at intervals of 5–15 min throughout the 2-hr period of exposure. A single determination of concentration was made at each interval by gas chromatography.

For chromatography we used a Gow Mac model 750 gas chromatograph equipped with a 30-m-long, fused silica open tubular capillary (0.53-mm internal diameter) column coated with a 5- μ m-thick layer of methylsilicone oil (J & W Scientific DB-1). A nitrogen carrier stream of 2–6 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop. The chromatograph was calibrated with secondary tank standards that had been calibrated with primary standards produced by injection of a liquid aliquot of anesthetic into a flask of known volume.

Because the concentrations of I-653 required to produce anesthesia exceeded the linear range of our

gas chromatograph, we reduced the concentration into the linear range by diluting each sample by a factor of 10. This dilution was accounted for in the calculation of concentration.

Throughout study, the temperature of all rats was maintained between 37.5 and 38.5°C by applying heat (infrared lamps) or cold (ice) to the outside of the chambers. Carbon dioxide and oxygen concentrations were measured twice during each run. Typically, carbon dioxide concentrations varied between 0.6 and 1.5%, as measured by infrared analysis with a Beckman LB-2 analyzer. Oxygen concentrations never decreased below 75%, according to a Beckman E2 Pauling meter, calibrated with nitrogen and oxygen at the beginning of each exposure.

At the end of the period of anesthetic/no anesthetic exposure, the reservoir bag was removed and 100% oxygen was flushed through the system for 5–10 min. The rats were then removed from the chambers and placed in individual Plexiglas boxes to complete their recovery. They were then returned to their wire-mesh cages until the next exposure period.

For 2 consecutive weeks, each rat was subjected to this protocol on Monday, Wednesday, and Friday for a total of six 2-hr exposures. The order of exposure was rotated for the three groups such that, by the sixth exposure, all possible orders of exposure had been applied. Thus, for one series, the exposures were: C–F–I, C–I–F, F–C–I, F–I–C, I–C–F, and I–F–C, where C is control, F is isoflurane, and I is I-653.

Twenty-four hours after the last exposure, the rats were weighed and killed by administration of 100% carbon dioxide. An autopsy was performed by a pathologist (LDF). Specimens of brain (including the pituitary gland), lung, heart, liver, kidney, pancreas, and duodenum were taken and immediately placed in 10% buffered formalin. For each specimen, a slide was prepared and coded. All slides for a given tissue were randomized and examined by a pathologist (LDF) who was unaware of the treatment given each rat. All specimens were graded for the presence or absence of injury. Pulmonary tissue also was graded for acute and chronic pneumonia. Analysis of variance or χ^2 analysis was applied. We accepted $P < 0.05$ as statistically significant.

Results

The desired anesthetic concentrations were achieved rapidly in all cases. For I-653, the average concentration was $99.9 \pm 2.2\%$ of the desired concentration, and for isoflurane, $96.0 \pm 2.3\%$ (mean $\pm$ SD). The effect of each anesthetic was apparent soon after injection of anesthetic into the system and was asso-

Table 1. Weights of Rats

Group	Control	I-653	Isoflurane
<i>n</i>	16	16	16
Weights (g) ^a			
Starting	304 ± 13	299 ± 12	298 ± 11
Ending	362 ± 20	350 ± 16	358 ± 21
Difference	58 ± 19	52 ± 18	60 ± 18

^aValues are expressed as the mean ± SD.

ciated with a tendency toward a decrease in temperature, prevented as noted above.

All rats gained weight. The average weights at the start of the study did not differ among groups nor did the average weights at the end of the study (Table 1). The difference between the starting and ending weights also did not differ among groups (Table 1). No tissue injury could be ascribed to either of the two anesthetics (Table 2). Most tissues revealed no injury. Lung specimens were remarkable only for atelectasis. Atelectasis was distributed randomly among the groups and probably resulted from the administration of 100% carbon dioxide. Two rats in the control group had pneumonia, one chronic and the other acute. No evidence of pneumonia was apparent in rats in the two anesthetic groups.

The few specimens from other organs with histologic evidence of injury were randomly distributed among the specimens from all anesthetic groups. One control rat with evidence of brain injury had cerebral edema and cerebellar neuronal necrosis. A second control rat that had myocardial injury had a very small papillary muscle necrosis (estimated to be ten cells). Two rats given isoflurane who had myocardial injury had chronic inflammation without necrosis, one of the left ventricle and one of the right ventricle. One rat given I-653 had a very small myocardial infarct of the right ventricle.

Discussion

Our test for toxic effects had three elements calculated to reveal any tendency of I-653 or isoflurane to produce organ injury. First, a large total anesthetic dose was administered (19.2 MAC-hr), ten times larger than the clinical dose associated with an ordinary anesthetic. Second, this dose was given over the course of 2 weeks. If I-653 or isoflurane produced enzyme induction, which predisposed to injury by increasing the rate of metabolism, our approach might have revealed injury, especially to the liver. Third, these anesthetics were given in a closed circuit that applied dry soda lime for absorption. Had breakdown of these agents

Table 2. Percentage of Organs Showing Injury

Group	Control	Isoflurane	I-653
<i>n</i>	16	16	16
Brain (%)	6	0	0
Pituitary (%)	0 ^a	0	0
Heart (%)	6	12	6
Lung (%)	62	75	38
Atelectasis (%)	50	75	38
Liver (%)	0	0	0
Duodenum (%)	0	0	0
Pancreas (%)	0	0	0
Kidney (%)	0 ^a	0	0

^a*n* = 15.

by dry soda lime produced toxic products, we might have discerned injury.

In no comparison was the injury to tissues seen with I-653 greater than that found in the comparison groups (Table 2). The incidence of injury to most organs was zero in all three groups. The absence of any evidence of toxicity due to the administration of I-653 is consistent with our earlier finding that I-653 does not injure the liver, kidney, or lungs of hypoxic, enzyme-induced rats (7). However, the study populations we used for both experiments may have been too small to reveal infrequent or rare injury. Given the finding in the present study of a zero incidence of injury in 16 rats, we may be 95% confident that the true incidence of a toxic response to repeated high-dose exposure to I-653 is < 17.1% (i.e., it could be anywhere between 0 and 17.1%) (10). Larger groups of animals must be studied to increase the degree of confidence we have in asserting that this new anesthetic is not toxic. However, even if studies employing larger numbers of animals do not reveal a toxic effect (as in the present study), this would not exclude the possibility of toxicity in a different species, for example, human beings. Nonetheless, the results obtained in the present study are reassuring and indicate further study of this promising new anesthetic.

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Circulatory Effects of Isoflurane during Acute Hypercapnia

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WATTWIL LMT, OLSSON JG. Circulatory effects of isoflurane during acute hypercapnia. *Anesth Analg* 1987;66:1234-9.

Acute respiratory acidosis results in increases in cardiac output and in systemic and pulmonary arterial blood pressures. The aim of this investigation was to determine if isoflurane modifies these effects. Nine patients (ASA II or III) scheduled for major surgery took part in the investigation. After the induction of general anesthesia, CO₂ was added to the inspiratory gas mixture. After 15 min, ventilation with addition of CO₂ (PaCO₂ 8-9 kPa) isoflurane (3%) was added. Hemodynamic measurements were made to study the effects of acute hypercapnia and the effects of

isoflurane during hypercapnia. The addition of carbon dioxide resulted in increases in cardiac output, systemic and pulmonary arterial blood pressures, and right and left ventricular stroke work. The addition of isoflurane during hypercapnia decreased systemic arterial blood pressure, but pulmonary arterial blood pressure was unaffected, cardiac output and stroke volume did not change, and left but not right ventricular stroke work decreased. In conclusion, acute pulmonary hypertension induced by hypercapnia was not affected by isoflurane but, despite increased right ventricular stroke work, there were no signs of right ventricular failure.

Key Words: ANESTHETICS, VOLATILE—*isoflurane*. CARBON DIOXIDE—*hypercapnia*.

Acute respiratory acidosis induced by ventilation with a hypercapnic gas mixture results in a hyperkinetic circulation with increases in cardiac output and systemic arterial blood pressure (1-5). This is caused by stimulation of the sympathetic nervous system resulting in release of catecholamines from sympathetic nerve endings and from the adrenal glands (1,3,5,6). The direct effects of hypercapnia on the cardiovascular system include dilation of the arterioles and depression of the myocardium, but the indirect effects are sympathoadrenal stimulation and the net result is an increase in systemic arterial blood pressure and cardiac output (7).

Both acute respiratory and metabolic acidosis increase pulmonary vascular resistance and pulmonary perfusion pressure (8). The pulmonary vasoconstrictor response to respiratory acidosis is independent of sympathetic control (9). During normocapnia, isoflurane decreases systemic arterial blood pressure by reducing total peripheral resistance (10). However, pulmonary arterial blood pressure and pulmonary vascular resistance are not affected by isoflurane during normocapnia (11).

The aim of this investigation was to study the cir-

culatory effects of acute hypercapnia in anesthetized patients and to ascertain whether isoflurane modifies the effects on systemic and pulmonary circulation induced by respiratory acidosis.

Methods

Nine patients (mean age 61 ± 6 yr) scheduled for major abdominal and thoracic surgery took part in the investigation. The research procedure was approved by the Ethics Committee of the Örebro County Council and the patients received both verbal and written information about the study and gave their consent to participate. All patients belonged either to ASA category II or III. Two patients were under treatment for hypertension, one with clonidine and one with bendroflumethiazide. One patient with a myocardial infarction 3 years previously was being treated with metoprolol. All patients were premedicated with a morphine derivative (Oxicon) 7.5-10.0 mg and hyoscine 0.3-0.4 mg IM 1 hr before the start of the investigation. Before induction of anesthesia a radial artery was cannulated and a thermodilution pulmonary artery catheter (American Edward's Lab) was inserted percutaneously via a cubital vein. All vascular cath-

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Editor's Note: American readers should bear in mind that kPa, as employed in the present article, is the international (SI) unit for measurement of partial pressures used throughout much of the rest of the world. A kPa of 5.4 equals a PCO₂ of about 40 mm Hg; a kPa of 9 equals a PCO₂ of about 67 mm Hg.

Table 1. Hemodynamic Variables and PaCO_2

	A	P Value	B	P Value	C	P Value	D
HR (beats/min)	74 ± 15	—	74 ± 11	—	75 ± 14	—	77 ± 18
SV (ml)	80 ± 19	< 0.01	61 ± 10	< 0.05	74 ± 17	—	72 ± 16
SAP (mm Hg)	136 ± 14	< 0.001	99 ± 20	< 0.001	126 ± 16	< 0.001	90 ± 15
DAP (mm Hg)	79 ± 8	< 0.01	64 ± 12	< 0.001	75 ± 14	< 0.001	57 ± 8
SPAP (mm Hg)	27 ± 7	< 0.05	22 ± 5	< 0.001	41 ± 7	—	41 ± 7
DPAP (mm Hg)	12 ± 2	—	11 ± 3	< 0.001	20 ± 5	—	20 ± 4
CVP (mm Hg)	6 ± 2	—	7 ± 2	< 0.001	11 ± 2	—	11 ± 2
PCWP (mm Hg)	7 ± 2	—	7 ± 1	< 0.01	11 ± 2	—	12 ± 3
PPP (mm Hg)	10 ± 4	—	7 ± 3	< 0.001	16 ± 5	—	14 ± 4
PaCO_2 (kPa)	5.5 ± 0.4	< 0.01	4.9 ± 0.5	< 0.001	8.6 ± 0.9	—	8.9 ± 1.0

A, Baseline values before anesthesia; B, after induction of anesthesia; C, after addition of CO_2 ; D, after addition of isoflurane during hypercapnia. Values are presented as mean ± SD; $n = 9$. See text for abbreviations.

eters were filled with normal saline and connected to pressure transducers (Gould, Electronics BV, Bithoven). Electrocardiogram (ECG), heart rate (HR), systolic and diastolic arterial blood pressures (SAP and DAP, respectively), systolic and diastolic pulmonary arterial blood pressures (SPAP and DPAP, respectively), and central venous (CVP) and pulmonary capillary wedge pressures (PCWP) were monitored throughout the study. Cardiac output (CO) was measured by the thermodilution technique (Cardiac Output Computer, model 9520A, American Edward's Lab) using chilled (below 4°C) 5% glucose solution. Each estimation of cardiac output was the mean of three determinations. Blood samples were taken from the radial artery catheter for determination of blood gas tensions. End-tidal PCO_2 (PETCO_2) was recorded continuously (Datex Instrumentarium Corp).

Using standard formulas, the following parameters were calculated: mean arterial blood pressure (MAP), mean pulmonary blood pressure (MPAP), systemic and pulmonary vascular resistance (SVR and PVR, respectively), right and left ventricular stroke work (RVSW and LVSW, respectively) and pulmonary perfusion pressure (PPP).

Procedure

After placement of monitoring devices, the patients rested for 15 min before baseline circulatory measurements and measurement of blood gas tensions. General anesthesia was induced with thiopental (4–5 mg/kg) and fentanyl (3 µg/kg) followed by pancuronium bromide for tracheal intubation. The patients were ventilated (Engström Respirator 300) with $\text{O}_2/\text{N}_2\text{O}$ (50/50) to maintain PETCO_2 at about 5%. When a circulatory steady state was established circulatory and blood gas measurements were repeated. Carbon dioxide (0.6–0.8 L/min) was then added to the inspiratory gas mixture to stabilize PETCO_2 at about 8–9%. After

15 min of ventilation with this addition of carbon dioxide all measurements were repeated, after which 3% isoflurane together with CO_2 was added to the inspiratory gas mixture for 5 min before new measurements were carried out. The study was completed before the start of surgery.

Statistics

Paired Student's *t*-tests were used for statistical analysis of the results, which are presented as means ± SD. A *P*-value of <0.05 was considered statistically significant.

Results

Effects of Anesthesia Induction

The induction of anesthesia caused significant decreases in cardiac output, stroke volume, systemic and pulmonary arterial blood pressure, and right and left ventricular stroke work (Fig. 1 and 2, Table 1). PaCO_2 changed from 5.5 ± 0.4 to 4.9 ± 0.5 kPa.

Effects of Carbon Dioxide

During the addition of carbon dioxide, PaCO_2 increased from 4.9 ± 0.5 to 8.6 ± 0.9 kPa. This was associated with significant increases in cardiac output, systemic and pulmonary arterial blood pressures, and right and left ventricular stroke work. PCWP, CVP, PPP and PVR also increased significantly but SVR remained unchanged (Fig. 1 and 2, Table 1).

Effects of Isoflurane

The addition of 3% isoflurane for 5 minutes in combination with hypercapnia (PaCO_2 8.9 ± 1.0) resulted in an immediate decrease of systemic arterial blood

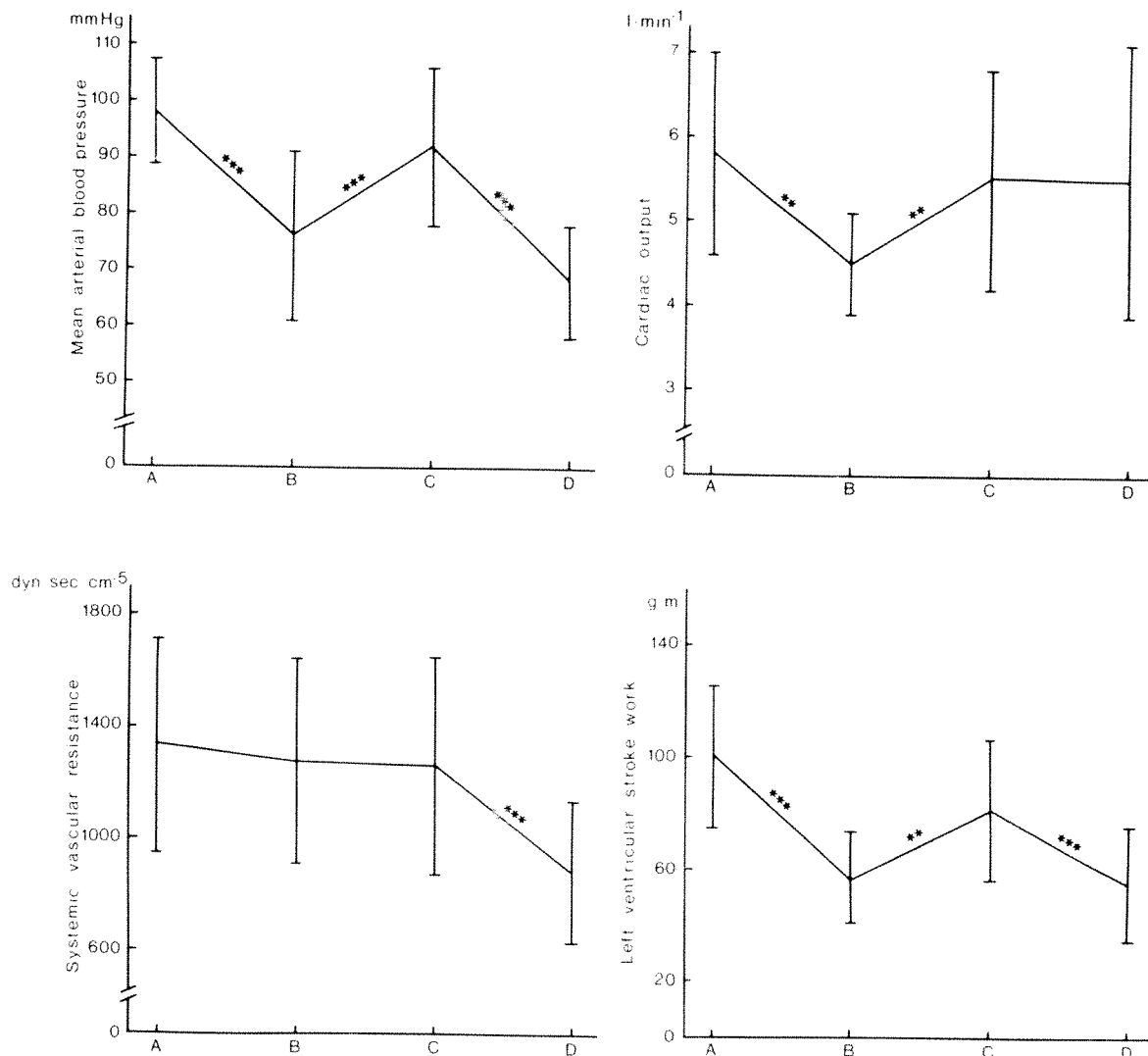


Figure 1. Changes in circulatory variables on the left side of the heart. A, Baseline values before anesthesia; B, after induction of anesthesia; C, after addition of carbon dioxide (PaCO_2 8.6 kPa); D, after addition of isoflurane during hypercapnia; Values are presented as mean $\pm$ SD; $n = 9$. Statistical comparisons are made between two adjacent values. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

pressure, but pulmonary arterial blood pressure was unaffected. Cardiac output and stroke volume did not change, and LVSW but not RVSW decreased (Fig. 1 and 2, Table 1). There were no ventricular extrasystoles during the addition of carbon dioxide alone or during the addition of carbon dioxide and isoflurane. After the induction of anesthesia FI_{O_2} was 0.5 and PaO_2 was above 20 kPa in all patients.

Discussion

The response to hypercapnia in our ASA II or III patients corresponded to that reported in other studies

of similar patients (3-5). The addition of carbon dioxide was accompanied by an increase in both systemic and pulmonary arterial blood pressures and in cardiac output. This led to a considerable increase in both left and right ventricular stroke work. Compared with the values after induction of anesthesia, RVSW increased about 130% and LVSW 30%. However, only RVSW exceeded (30%) the baseline levels. If pulmonary vascular resistance is low, the right ventricle is not required for adequate cardiac output to be maintained (12,13). However, if pulmonary vascular resistance is elevated, then the right ventricle must act as a pump to maintain the circulation (14). Right-sided heart failure is usually associated with low cardiac output and a pressure higher in the right than in the left atrium (14). During the addition of carbon dioxide, pulmonary vascular resistance increased almost twofold but there were no signs of right ventricular failure.

The addition of isoflurane during hypercapnia was

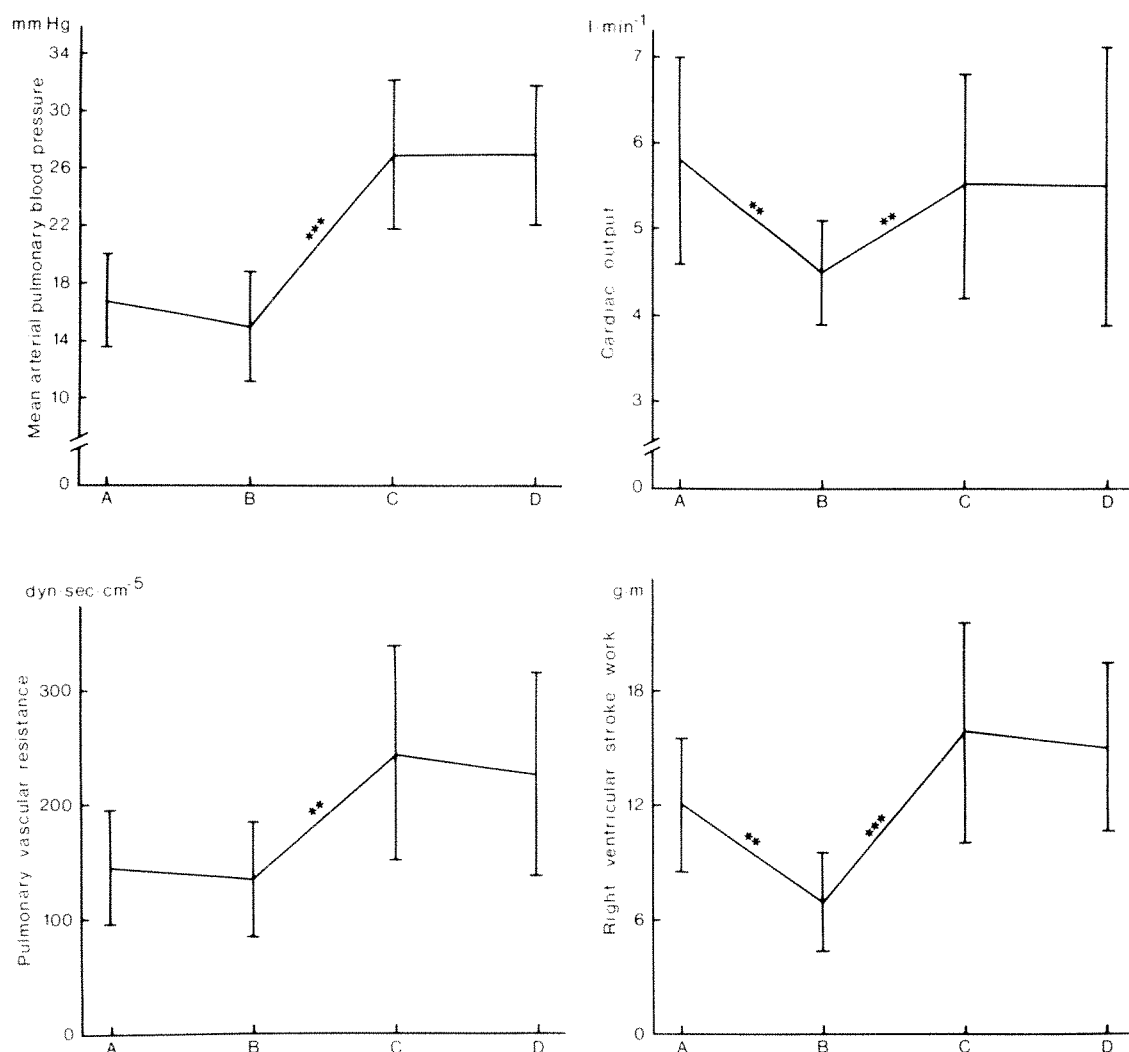


Figure 2. Changes in circulatory variables on the right side of the heart. Abbreviations as in Figure 1.

accompanied by an immediate and progressive decrease of the systemic arterial blood pressure. Systemic vascular resistance decreased but cardiac output was unchanged and, therefore, the decrease in SVR was the result of vasodilation. It has been shown that the concomitant use of nitrous oxide and isoflurane produces less hypotension than does isoflurane alone, but heart rate, stroke volume, and cardiac output remain unaffected (15). Therefore higher blood pressures after addition of nitrous oxide result from increased peripheral resistance (15). In our study the effects of nitrous oxide were not evaluated. As afterload diminished with unchanged stroke volume, left ventricular stroke work was reduced after the addition of isoflurane. The hemodynamic effects of isoflurane during hypercapnia with a decrease in SAP

but with unchanged CO resemble those described during normocapnia (10). However, during isoflurane anesthesia in younger patients stroke volume often decreases but, despite the decrease in stroke volume, cardiac output is often maintained as heart rate increases (10). In our present study of older patients, stroke volume and heart rate did not change during the addition of isoflurane. Therefore the effects of isoflurane on SV and HR during hypercapnia in elderly patients resemble those during normocapnia in elderly patients, there being often only minimal changes in HR and SV during isoflurane anesthesia in elderly patients (16). The cause of vasodilation produced by isoflurane is not completely understood. Among several theories the following have been mentioned: 1) decreased tone and contractility of the smooth muscle in the peripheral vascular bed (17), 2) decreased sensitivity of the vascular smooth muscle to changes in sympathetic activity (18), and 3) dose-dependent depression of the autonomic nervous system (18).

During acute hypercapnia, circulating catecholamine levels increase (5,6), as do systemic blood pressure and cardiac output. In the present study, systemic arterial blood pressure increased during hypercapnia because of the increase in cardiac output as systemic vascular resistance was unchanged. If isoflurane decreases activity of the sympathetic nervous system with reduction of circulating levels of catecholamines, cardiac output should also have been reduced. Consequently the direct effect of isoflurane on the systemic vascular bed seemed to predominate during the hyperkinetic conditions in the present study.

During normocapnia, isoflurane has little or no effect on pulmonary hemodynamics in clinical or experimental studies (11). In contrast to the effects on the systemic vascular bed, addition of 3% isoflurane for 5 min in the present study did not affect the increased pulmonary arterial pressure or pulmonary vascular resistance induced by hypercapnia. PVR is dependent on the pulmonary perfusion pressure and on flow through the pulmonary vascular bed. During the hypercapnic period isoflurane affected neither pulmonary vascular flow nor perfusion pressure and, with unchanged PVR, it can be concluded that isoflurane had no direct effect on the pulmonary vascular bed. Consequently the effects of isoflurane are different in the systemic and in the pulmonary vascular bed during hypercapnia. However, the mechanism behind the increase in systemic and pulmonary arterial blood pressure during hypercapnia is also different. The increase in systemic arterial blood pressure is caused by increased sympathoadrenal activity (5,6), but the increase in pulmonary arterial blood pressure is independent of sympathetic control (9). The pulmonary vasoconstrictor response is probably mediated by the direct action of H^+ or CO_2 on the pulmonary smooth muscle (9).

As mentioned earlier, isoflurane reduced systemic vascular resistance and left ventricular stroke work. However, pulmonary vascular resistance and right ventricular stroke work were not diminished during the addition of isoflurane and remained high. Despite this load on the right ventricle, there were no signs of failure measured as an increased CVP or diminished CO. Consequently in these ASA II and III patients, isoflurane had no negative effect on right ventricular work despite the strongly increased afterload induced by hypercapnia. However, isoflurane was added for only 5 minutes. If 3% isoflurane is administered for a longer period the risk of right heart failure is probably high.

During acute respiratory acidosis, circulating levels of catecholamines increase (1,3,5,6). In the study by

Rasmussen et al., a $PaCO_2$ of about 9 kPa caused plasma epinephrine levels to double and norepinephrine levels to triple (5). Because $PaCO_2$ was almost the same in our study during hypercapnia, we probably had a similar increase in catecholamine levels. Despite increases in circulating levels of catecholamines, there were no ventricular extrasystoles during the hypercapnic period before or during the addition of isoflurane. A major advantage of isoflurane is that indeed it does not sensitize the myocardium to catecholamines (19).

In summary, acute hypercapnia with $PaCO_2$ of about 9 kPa resulted in a hyperkinetic circulation with increases in pulmonary and systemic arterial blood pressures, cardiac output, and both right and left ventricular stroke work. The addition of isoflurane during this level of hypercapnia immediately reduced systemic but not pulmonary arterial blood pressure. Cardiac output and heart rate were not affected by isoflurane and thus LVSW but not RVSW was reduced. However, despite the increase in afterload induced by hypercapnia, there were no signs of right ventricular failure during the addition of isoflurane.

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Comparison of the Effects of Halothane on Newborn and Adult Rabbit Myocardium

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KRANE EJ, SU JY. Comparison of the effects of halothane on newborn and adult rabbit myocardium. *Anesth Analg* 1987;66:1240-4.

The effect of halothane on myocardial contractility was studied in isolated right ventricular muscle preparations from newborn and adult rabbits. Right ventricle strips were mounted in oxygenated Krebs' solution and stimulated with supramaximal voltages at 1.0 Hz, while isometric force of contraction was continuously recorded. Halothane (0.4, 0.7, and 1.1%) caused a significant dose-dependent depression of both peak developed tension (42, 61, and 70%, respectively) and maximum rate of rise of isometric tension (40, 56, and 64%, respectively) of newborn myocardium. New-

born myocardial preparations exhibited approximately 20% greater depression of contractility than adult myocardium at each concentration studied ($P < 0.05$), thus a parallel shift of the dose-response curves was observed. It was concluded that halothane exerts a potent depressant effect on newborn myocardium that is greater than that on adult myocardium. The depressant effect of halothane on the newborn myocardium may contribute to its hypotensive effect in newborn infants.

Key Words: ANESTHESIA—pediatric. ANESTHETICS, VOLATILE—halothane. HEART—myocardial function.

Halothane commonly produces hypotension in both newborn infants (1,2) and adult patients (3). Clinical impressions suggest that newborns are more prone to halothane-induced hypotension than adults, (4) although direct comparison of the degree of hypotension induced by equivalent anesthetic doses in infants and adults has not been reported. Anesthetic-induced hypotension may be caused by a direct depressant effect of volatile anesthetics on the myocardium (5) or vascular smooth muscle (6), an indirect effect mediated by the autonomic nervous system (7), or a combination of these effects. Although halothane has been shown to decrease cardiac output and blood pressure in human infants (8) and newborn pigs (9), the mechanism for this observation is not clear.

Rao and co-workers recently reported that newborn atrial heart muscle from the rat is more sensitive to the negative inotropic effect of halothane than adult atrial myocardium (10). However, in other studies, atrial and ventricular myocardium have not re-

sponded similarly to other negative inotropic drugs (11,12), and ventricular function probably is a more important determinant of cardiac performance than atrial function.

Therefore, the purposes of this study were to determine the extent to which halothane directly depresses contractility of newborn ventricular myocardium and to compare this depression to that in adults. To eliminate the effects of the peripheral vasculature and autonomic nervous system on myocardial performance, we used an isolated myocardial strip preparation.

Methods

Newborn New Zealand white rabbits of either sex (age, 1-4 days, weight, 54-97 g) were killed by decapitation. Young adult males of the same species (2-3 months, 1.7-2.6 kg) were killed by cervical dislocation. The hearts were quickly removed and placed in oxygenated modified Krebs' solution (see later), and strips (approximately 2-3 mm in width and 5-10 mm in length) were rapidly dissected from the free right ventricular wall parallel to the axis of the heart. The ventricular strips were mounted in a Blinks' dual tissue bath (13). One end of the ventricular strip was attached with a clip to a punctate platinum stimulating electrode and the other end was attached with a 4-0 silk thread to a calibrated Statham G7B force trans-

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ducer. Ventricle strip preparations were chosen for this work after several unsuccessful attempts to isolate papillary muscle from the right ventricle of newborn hearts. The right ventricle was chosen to minimize the thickness of the myocardial preparations.

The bathing solution contained modified Krebs' solution oxygenated with 95% O₂-5% CO₂, at 30°C, pH 7.40. The composition of the Krebs' solution (in mM) was NaCl, 121; KCl, 2.4; CaCl₂, 2.5; MgSO₄, 1.2; NaHCO₃, 24.8; KH₂PO₄, 1.2; and glucose, 5.6. Newborns and adults were studied simultaneously to ensure identical conditions. Bathing solutions were maintained at 30°C to increase preparation stability compared to 37°C (14). Preparations were paced with DC square wave impulses of 4 msec duration at 1.0 Hz, 50-100% above the threshold voltage, using a Grass S88 stimulator. The muscle length was adjusted to obtain maximum developed tension. Isometric twitch tension was continuously displayed on a Gould 2400S four-channel recorder. Peak developed isometric tension and maximum rate of rise of peak developed tension (dF/dt_{max}) were analyzed. A stabilization period of up to 1 hr was allowed before any intervention, at which time peak developed tension had reached a steady state. We found that the twitch tension of newborn and adult preparations remained relatively stable ($\pm 10\%$) over 3 hr; therefore all experiments were carried out within this time period.

Experimental Procedure

After the initial stabilization period, each preparation was exposed to three concentrations of halothane, 0.4, 0.7, and 1.1%, in random sequence. Halothane was delivered into the 95% O₂-5% CO₂ mixture with a calibrated anesthetic vaporizer, and the concentrations in the bathing solution were assayed by gas chromatography (15). The partial pressures of halothane in the bathing solution are expressed as the percentage of 1 atm.

Measurements of myocardial function were made: 1) before exposure of the preparations to halothane (Control 1), 2) during exposure to halothane when peak developed tension reached a new steady state, and 3) after discontinuation of halothane when isometric tension recovered to prehalothane values (Control 2). The effects of halothane on isometric tension and maximum rate of rise of tension were expressed as the percentage of the mean of the two controls before (Control 1) and after (Control 2) each halothane administration. This procedure was repeated for the second and third halothane concentrations.

At the end of each experiment, the length, width,

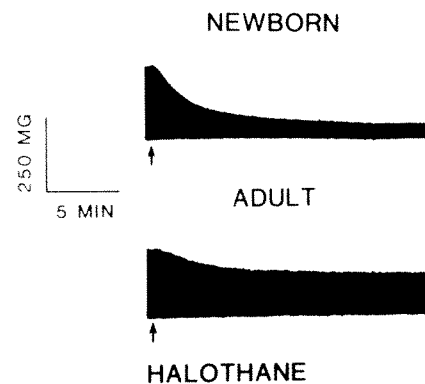


Figure 1. Tracings comparing the effect of halothane (0.7%) on isometric twitch tension of two ventricular preparations in the same tissue bath, newborn (top) and adult (bottom). A greater depression of the twitch tension occurs in the newborn than in the adult.

and weight of each muscle preparation was measured. The cross-sectional area of each muscle was then calculated (weight/length), assuming a tissue density of 1.0 g/cm³.

The effect of halothane was compared to control by Student's *t*-test for paired data. The effects of halothane on newborn and adult myocardium were expressed as the percentage of control, which were converted to a normal distribution with the arc sine transformation (16), and then compared using Student's *t*-test for unpaired data. The arc-sine transformation was used because proportional changes in two small populations were being compared. The slopes of the dose-response curves for newborns and adults were compared by deriving the slopes of dose-response curves for each animal with linear regression analysis, then using the unpaired Student's *t*-test to compare the slopes of newborns to adults. A *P* value of <0.05 was considered statistically significant.

Results

Adult preparations exhibited a peak developed tension of 182 ± 25 mg/mm² (mean $\pm$ SEM, $n = 14$ preparations from seven rabbits). Newborn preparations exhibited peak developed tension of 116 ± 20 mg/mm² ($n = 13$ preparations from 13 rabbits), which is 64% that of the adult, at comparable cross-sectional areas (3.88 ± 0.45 vs 3.22 ± 0.86 mm², respectively).

Halothane (0.4, 0.7, 1.1%) caused a significant depression of peak developed tension in both newborn and adult preparations (Fig. 1). The onset of halothane-induced depression was rapid, reaching maximal effect within 5 min and steady state within 10-20 min of exposure. This effect was fully reversible (Fig. 2). The peak developed tension of both adult and newborn preparations recovered to $104 \pm 5\%$ of

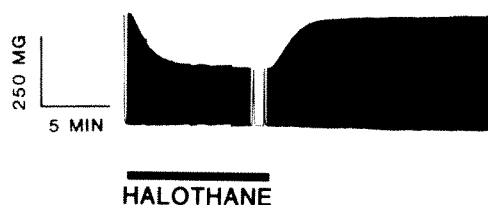


Figure 2. A typical tracing showing the effect of halothane (0.7%) and its reversibility on isometric twitch tension of an adult right ventricular strip preparation. Halothane decreased peak developed tension rapidly, which reached steady state within 10 min. Twitch tension returned to prehalothane state within 15 min after discontinuation of halothane.

prehalothane values within 15–30 min after discontinuation of halothane.

Isometric tension of newborn myocardium was more depressed by halothane than that of the adult, but with a similar time course of depression and recovery. The effect was dose dependent for both peak-developed isometric tension (Fig. 3) and rate of rise of isometric tension (Fig. 4). The effects of halothane (0.4, 0.7, 1.1%) on peak-developed tension of newborn myocardium were (mean $\pm$ SEM, percentage of control) 57.8 ± 4.4 , 38.9 ± 3.2 , and $29.8 \pm 2.0\%$, respectively, whereas the effects on adult myocardium were 71.4 ± 2.5 , 50.2 ± 2.1 , and $40.9 \pm 2.0\%$, respectively. The effects of halothane (0.4, 0.7, 1.1%) on maximal rate of rise of tension of newborn myocardium were 60.1 ± 3.0 , 43.8 ± 2.8 , and $35.7 \pm 2.0\%$, respectively, whereas the effects on adult myocardium were 73.5 ± 2.3 , 54.3 ± 1.9 , and $44.5 \pm 2.0\%$, respectively. Differences in both measures of myocardial contractility between newborn and adult were statistically significant at each concentration.

The slopes of the dose-response curves of newborn and adult myocardium were similar for each parameter of contractility.

Discussion

This study shows that in vitro adult right ventricle generated higher isometric tension per unit cross-sectional area than did newborn right ventricle, and that clinical concentrations of halothane produced more significant in vitro depression of myocardial contractility in newborn than in adult heart.

The higher peak-developed tension per cross-sectional area of adult right ventricular strips than newborn preparations is consistent with a reduction of active tension generated by cardiac muscle from fetal and newborn lamb (18) and newborn puppy (19), compared to adults of the same species. This may be

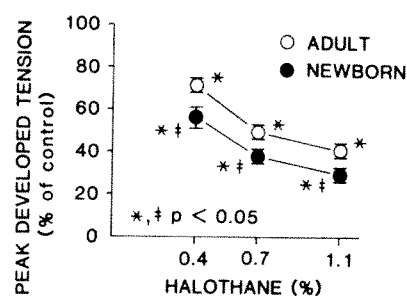


Figure 3. Dose-response curves (mean $\pm$ SEM) for the effect of halothane on the peak-developed tension of adult ($n = 14$) and newborn ($n = 13$) right ventricle strip preparations. * $P < 0.05$ compared to control. † $P < 0.05$ compared to adult.

explained by the fact that the newborn heart contains fewer numbers of contractile units per mass of tissue than adult heart (20) and that the proportion of non-contractile mass (cell nuclei, mitochondria, and surface membranes) in immature heart (70%) is greater than in adult heart (40%) (21). If force of contraction per cross-sectional area is normalized for proportion of contractile mass, newborn and adult hearts are capable of similar force generation (22).

The responses of adult right ventricular preparations to halothane found in the present study are comparable to those of adult rabbit papillary muscle previously published from other laboratories (22) and our laboratory (23) (for example, 56% depression by 0.8% halothane [23], vs 50% depression by 0.7% halothane in the present study). Halothane depression of newborn myocardial contractility in our study is comparable to that observed by Rao et al. (10). Using a different model (rat right atrium, paced at 3.3 Hz at 30°C), they found the concentrations of halothane necessary to produce 50% depression (ED_{50}) to be 0.82% for the adult and 0.44% for the newborn, compared with 0.7 and 0.5%, respectively, in the present study.

Halothane therefore causes a greater proportional decrease in the strength of myocardial contraction of the newborn than the adult, superimposed on smaller force generation of the newborn heart in the absence of the depressant effect of halothane. Morphologic differences alone between adult and newborn heart cannot account for the greater sensitivity to halothane of the newborn. It would be interesting to determine if the greater sensitivity of newborn ventricular myocardium is pacing-rate-dependent, although Lynch (24) found that halothane depression of fast action potential peak tension development and maximal rate of tension development of adult guinea pig papillary muscle is not frequency dependent between 0.1 and 3 Hz.

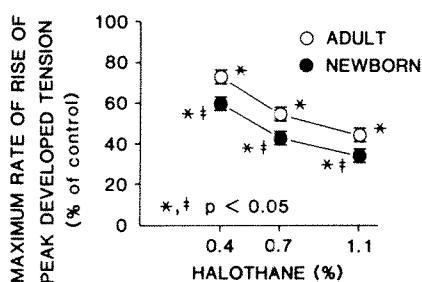


Figure 4. Dose-response curves (mean $\pm$ SEM) for the effect of halothane on the maximal rate of rise of developed tension of adult ($n = 14$) and newborn ($n = 13$) right ventricle strip preparations. * $P < 0.05$ compared to control. † $P < 0.05$ compared to adult.

Both newborn and adult myocardial fibers were stretched to achieve maximal force of contraction before exposure to halothane, assuring that experimentation was begun at equivalent points on the length-tension curve. We did not determine if exposure to halothane alters the position or shape of the length-tension curve differently in newborn and adult myocardium, which could possibly account in part for the greater depression of contractility in the newborn.

The cellular mechanism of halothane-induced myocardial depression in the newborn is not known. Because halothane and other halogenated anesthetics are highly lipid soluble, they are theoretically capable of interfering with membrane function and other intracellular processes associated with muscle contraction. Different cellular lipid composition or different intracellular proportion of lipid and water in newborn myocardium might lead to an alteration in intracellular halothane concentration, which itself might in part account for differences in sensitivity to halothane in the newborn (25). Or one or more subcellular loci of halothane depression may be particularly sensitive in the newborn. In adult cardiac muscle, halothane has been shown to decrease slow inward calcium (Ca^{2+}) currents across the sarcolemma (24,26,27), to depress actomyosin Ca^{2+} -ATPase activity (28), myofibrillar ATPase activity (29), and maximal Ca^{2+} -activated tension development of the contractile proteins (30), and to alter sarcoplasmic reticulum function (31,32). Any one or more of these sites may be particularly sensitive in the newborn.

Because the newborn relies more on sarcolemmal Ca^{2+} current than the adult for derivation of intracellular Ca^{2+} required for activation of contraction (33,34), halothane inhibition of sarcolemmal currents may be of particular importance in the newborn. This speculation is based on evidence that sarcoplasmic reticulum of the newborn myocardium is less devel-

oped and contains less Ca^{2+} than adult myocardial sarcoplasmic reticulum (20,35), the T-tubule system and terminal cisternae are less prominent in the newborn than in the adult rabbit (20), and the newborn myocardium is less sensitive than the adult to the depressant effects of ryanodine, a potent inhibitor of cardiac sarcoplasmic reticulum Ca^{2+} uptake and release (33).

Halothane results in depletion of sarcoplasmic reticulum Ca^{2+} stores (31,32). Because newborn myocardium contains less sarcoplasmic reticulum than adult myocardium (20), significant reduction of newborn intracellular Ca^{2+} stores may occur in the presence of halothane.

Previous results from our laboratory demonstrate a slight depression of Ca^{2+} -activated tension generation in muscle fibers with mechanically disrupted cell membranes by higher concentrations of halothane than are clinically used (30), suggesting halothane depression of actomyosin ATPase (28,29) is probably not of major importance in adult myocardium. However, it may assume a larger role in explaining depression of newborn myocardium. Two age-dependent isoenzymes of cardiac myosin-heavy chain have been identified (36,37); the myosin isoenzyme predominantly present in newborn cardiac muscle (V_1) has slower Ca^{2+} -dependent ATPase activity than the adult isoenzyme (V_3) (36). The functional significance of newborn myosin isoenzymes, and their response to halothane, remain to be tested.

Several factors may operate synergistically to produce the effects that we observed in the newborn. For example, small changes in sarcolemmal Ca^{2+} flux or SR Ca^{2+} storage may be amplified by the increased sensitivity of the newborn myocardial cell to Ca^{2+} , a consequence of its smaller volume of myoplasm and lesser Ca^{2+} buffering (20), and increased myofibrillar sensitivity to Ca^{2+} (38). Thus a small halothane-induced reduction of intracellular Ca^{2+} could markedly depress contractility. Alternatively, a small decrease in myoplasmic Ca^{2+} concentration from a decrease in transsarcolemmal Ca^{2+} flux or decreased sarcoplasmic reticulum Ca^{2+} release, and a small change in the activity of Ca^{2+} -activated contractile proteins, could together produce marked depression of myocardial contractility.

In summary, newborn rabbit myocardial preparations are capable of less tension generation than are adult rabbit myocardial preparations. Clinical concentrations of halothane depress isometric twitch tension and the rate of tension development of both newborn and adult rabbit hearts. The degree of myocardial depression was 20% greater in newborn than in adult preparations at all concentrations tested. We conclude

that greater halothane-induced myocardial depression of the newborn heart may be responsible for the greater hypotensive effect observed clinically in newborns. Delineation of the cellular mechanism of anesthetic depression of myocardial function in both newborns and adults may further our understanding of the cellular actions of general anesthetics and suggest clinically useful ways of predicting and treating drug-induced myocardial depression.

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Clinical Pharmacokinetics of Carbonated Local Anesthetics II: Interscalene Brachial Block Model

Radha Sukhani, MD, and Alon P. Winnie, MD

SUKHANI R, WINNIE AP. Clinical pharmacokinetics of carbonated local anesthetics II: interscalene brachial block model. *Anesth Analg* 1987;66:1245-50.

A double-blind comparison of 1.1% lidocaine carbonate and 1.0% lidocaine hydrochloride was carried out in 30 healthy adult patients undergoing upper-extremity surgery under interscalene brachial plexus block. Epinephrine (1:200,000) was added to both solutions just before injection. As compared to lidocaine hydrochloride, lidocaine carbonate produced, in addition to a 38% reduction in onset time, a remarkable increase in the extent of anesthesia: lidocaine carbonate

produced surgical anesthesia of the entire upper extremity including the hand in 87% of the patients, whereas lidocaine hydrochloride produced similar anesthesia in only 53% of the patients. Thus, supplemental blocks were required in 66% of the patients who received lidocaine hydrochloride, whereas they were required in only 25% of those who received lidocaine carbonate.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—interscalene brachial block. ANESTHETICS, LOCAL—lidocaine carbonate.

Early studies by Bromage and Gertel (1) and Schulte-Steinberg et al. (2), as well as more recent studies by the present authors (3), have demonstrated that carbonated local anesthetics have shorter latency periods than the equivalent hydrochloride salts when used for brachial plexus anesthesia. McClure and Scott (4) demonstrated not only shorter latency but also greater spread using carbonated bupivacaine, compared to bupivacaine hydrochloride for interscalene brachial plexus block. The present investigation was undertaken to determine whether lidocaine carbonate produces a similar increase in dermatomal spread compared with lidocaine hydrochloride. The interscalene technique of brachial plexus block seems to be an ideal model to evaluate extraneural spread, because the drug is deposited at the roots, and the number of dermatomes blocked becomes a function of the extent of diffusion of the local anesthetic.

Materials and Methods

This prospective, double-blind, randomized study was carried out in 30 healthy, consenting, adult patients

who were free of cardiovascular and neurologic disease and scheduled to undergo upper-extremity surgery under brachial plexus anesthesia. The interscalene technique of brachial plexus was carried out in each patient using a volume of local anesthetic equal in milliliters to half the patient's height in inches plus 2-4 ml.

Patients were classified into two equal groups, one group receiving 1.0% lidocaine hydrochloride and the other 1.1% lidocaine carbonate. Both solutions were commercial preparations. The seeming discrepancy in the two concentrations is because of the fact that equal volumes of 1.0% lidocaine hydrochloride and 1.1% lidocaine carbonate are equivalent in terms of lidocaine base. Times required for onset of and achievement of the final extent of analgesia and anesthesia were determined in the distribution of each of the nine dermatomes from C₂ through T₂. The solution of local anesthetic in each case was freshly drawn with epinephrine (1:200,000) added outside of the operating room by a pharmacist to conceal the identity of the drugs, because carbon dioxide bubbles out of the carbonated solution if allowed to stand. In all cases surgery was delayed for 20 mins after injection so that supplemental blocks of missed nerves could be carried out if necessary. The data were analyzed to compare the results in the two groups using Student's *t*-test and Fisher's exact probability test. A *P* value of <0.05 was considered statistically significant.

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Table 1. Patient Characteristics and Volume of Drug Used

Drug	Age (yr $\pm$ SD)	Height inches $\pm$ SD)	Weight (kg $\pm$ SD)	Volume injected (ml $\pm$ SD)
Lidocaine-HCl (n = 15)	35 $\pm$ 13.28	66 $\pm$ 0.32	72.53 $\pm$ 9.87	37.92 $\pm$ 1.54
Lidocaine-CO ₂ (n = 15)	39.40 $\pm$ 14.33	66 $\pm$ 0.32	73.80 $\pm$ 10.17	37.80 $\pm$ 1.10

Table 2. Spread of Local Anesthetic

Modality	Drug	Dermatomes blocked (% of patients in whom they were blocked)								
		C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈	T ₁	T ₂
Analgesia	Lidocaine-HCl	13	40	86	100	100	100	93	93	53
	Lidocaine-CO ₂	33	73	100	100	100	100	100	100	93
Anesthesia	Lidocaine-HCl	6	40	86	100	100	86	46	46	6
	Lidocaine-CO ₂	33	73	100	100	100	100	100 ^a	86 ^b	40 ^b

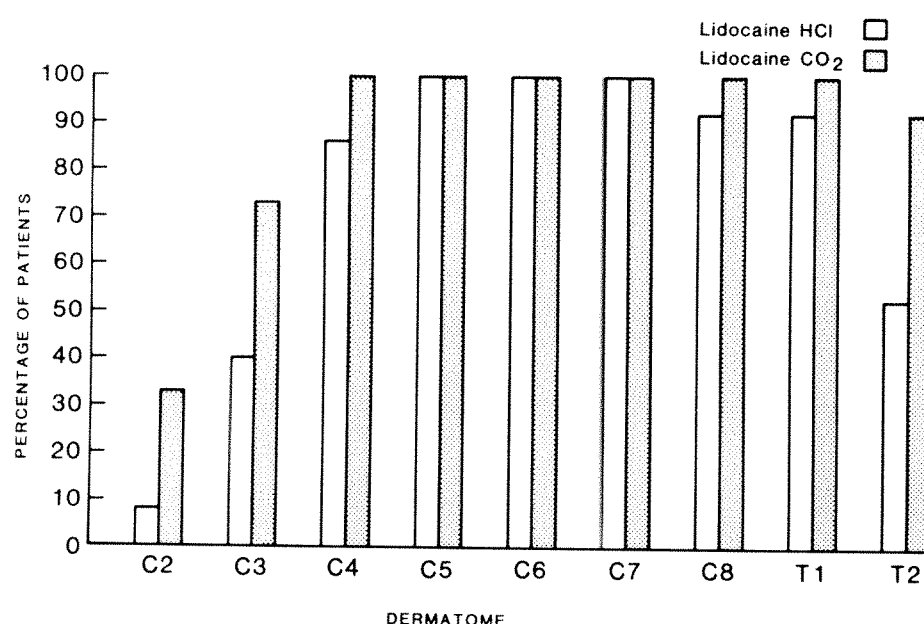
^a*P* $\leq$ 0.001.^b*P* $\leq$ 0.05.

Figure 1. Graphic representation of spread of the local anesthetic in terms of the percentage of patients who developed analgesia at each dermatome.

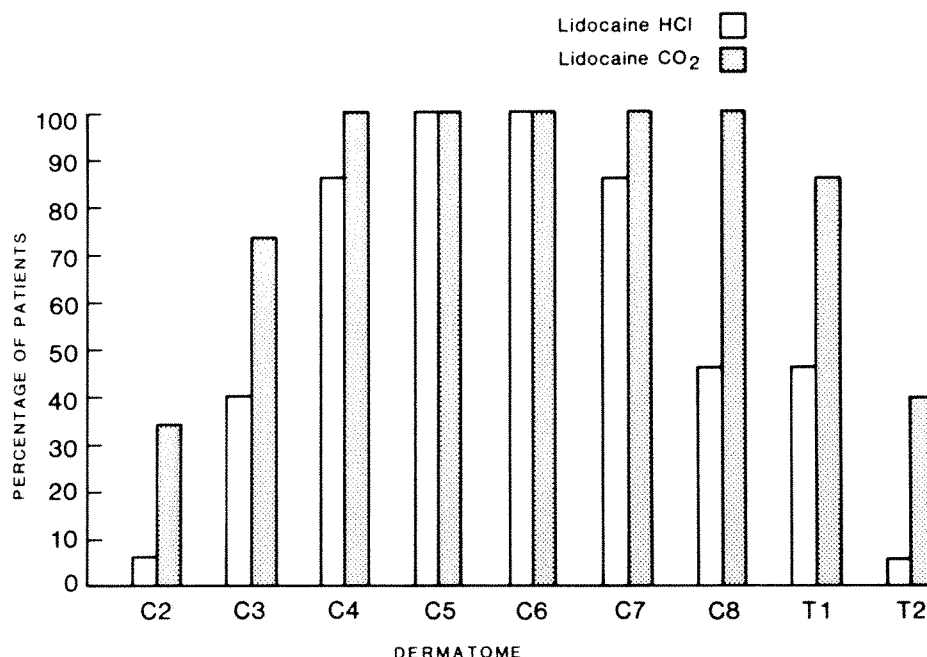
Results

The mean age, height, and weight of the patients in the two groups and the mean volume of the two solutions injected did not differ statistically (Table 1). The percentage of patients in each group that achieved analgesia and anesthesia of each dermatome is represented graphically in Figures 1 and 2, which are based on the data presented in Table 2. In the lidocaine carbonate group, analgesia was achieved in 100% of the patients in the distribution of C₄ through

T₁, whereas in the lidocaine hydrochloride group analgesia was achieved in 100% of the patients in the distribution of C₅ through T₇.

In the lidocaine carbonate group, surgical anesthesia of the fourth through eighth cervical dermatomes was achieved in 100% of patients, whereas in the hydrochloride group surgical anesthesia was achieved in only the fifth and sixth cervical dermatomes in 100% of patients. These data on the spread of the local anesthetic agents were analyzed statistically using Fisher's exact probability test, which in-

Figure 2. Graphic representation of spread of the local anesthetic in terms of the percentage of patients who developed anesthesia at each dermatome.



indicated that although there was no significant difference between the two groups with respect to analgesia, there was a significant difference with respect to anesthesia in the distribution of C₈, T₁, and T₂, the most frequently missed dermatomes with the interscalene technique. As a result of these differences, two-thirds of the patients in the hydrochloride group required supplemental nerve blocks, whereas only one-fourth of the patients in the carbonate group required supplemental blocks (Table 3).

The times of onset of analgesia and anesthesia in each dermatome following the injection of the two drugs are compared in Figures 3 and 4, which are based on the data in Table 4. Times to onset of analgesia and anesthesia were the shortest with both drugs, as would be expected, at the level of C₅, and increased progressively as the solution diffused away from the injection site. Onset times of both analgesia and anesthesia were shorter at each of the dermatomes where analgesia and/or anesthesia was achieved following lidocaine carbonate, but the differences were statistically significant only with respect to anesthesia and only at C₂, C₇, T₁, and T₂. Much more significant, both statistically and clinically, is the number of dermatomes blocked with relation to time. This is represented graphically in Figure 5, which indicates rather dramatically that the spread of anesthesia was statistically significantly faster with lidocaine carbonate than with lidocaine hydrochloride at 5, 10, 15, and 20 min.

Table 3. Patients Requiring Supplemental Blocks

Type of block	Drug	
	Lidocaine-HCl (n = 15)	Lidocaine-CO ₂ (n = 15)
Intercostobrachial (T ₂)	10 (66%)	4 (27%)
Ulnar (C ₈ , T ₁)	4 (27%)	2 (13%)
Total	14 (93%)	6 (40%)

Discussion

When the carbonate salt of a local anesthetic is used, carbon dioxide is released and rapidly diffuses throughout the tissues in the immediate vicinity, crossing cell membranes, lowering intracellular pH, and producing an electrochemical gradient that favors a greater uptake of local anesthetic base by the tissues. Furthermore, as the carbon dioxide diffuses away from the injection site, the resultant increase in pH promotes conversion of the local anesthetic to undissociated free base, increasing lipid solubility and enhancing the ability of the local anesthetic to penetrate cell membranes. And finally, carbon dioxide itself probably has a direct effect on the nerve membrane that contributes to the blocking process (5,6). Thus, a carbonate salt should result in an increase in both

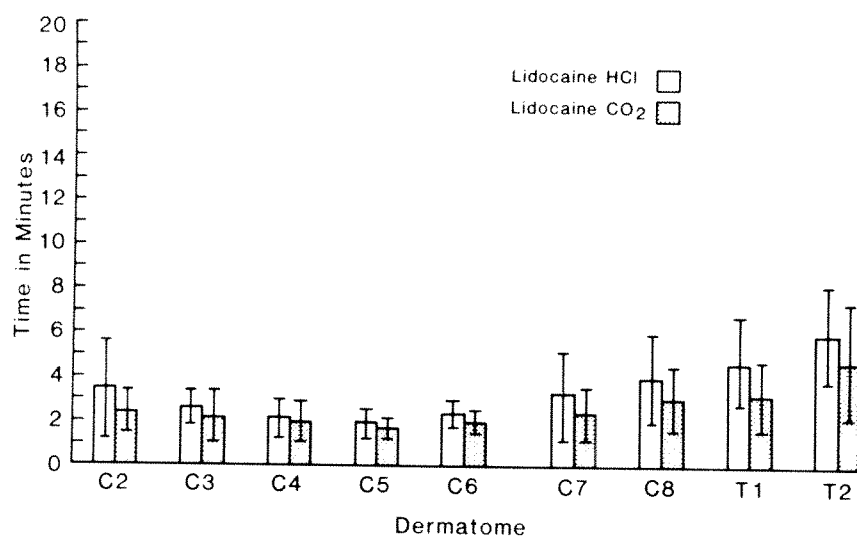


Figure 3. Graphic comparison of the time of onset of analgesia in each dermatome. There is no statistically significant difference between the two agents with respect to onset of analgesia.

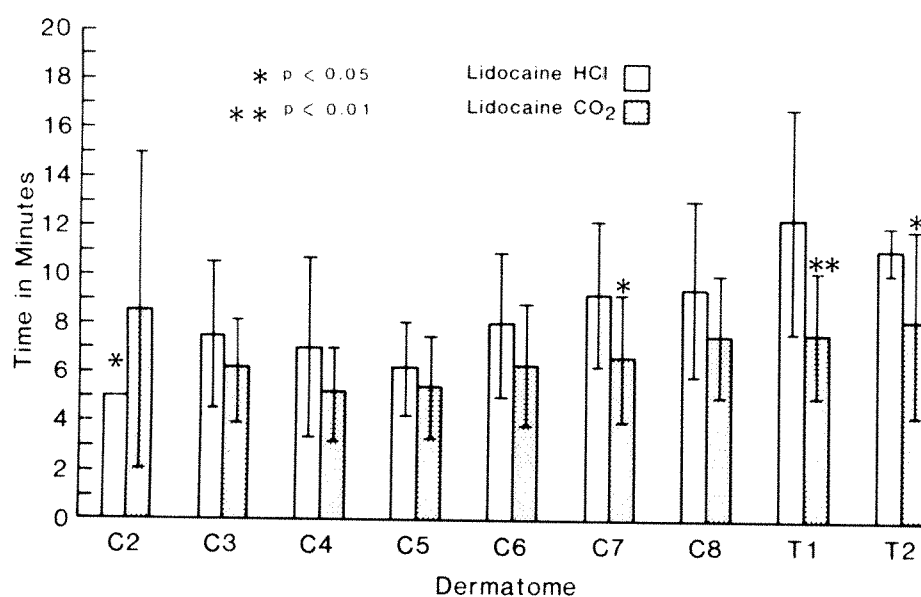


Figure 4. Graphic comparison of the time of onset of anesthesia in each dermatome. The difference between the two agents is statistically significant only in dermatomes C₇ ($P < 0.05$), T₁ ($P < 0.01$), T₂ ($P < 0.05$), and C₂ ($P < 0.05$), although anesthesia was achieved in only one patient (6%) in the hydrochloride group.

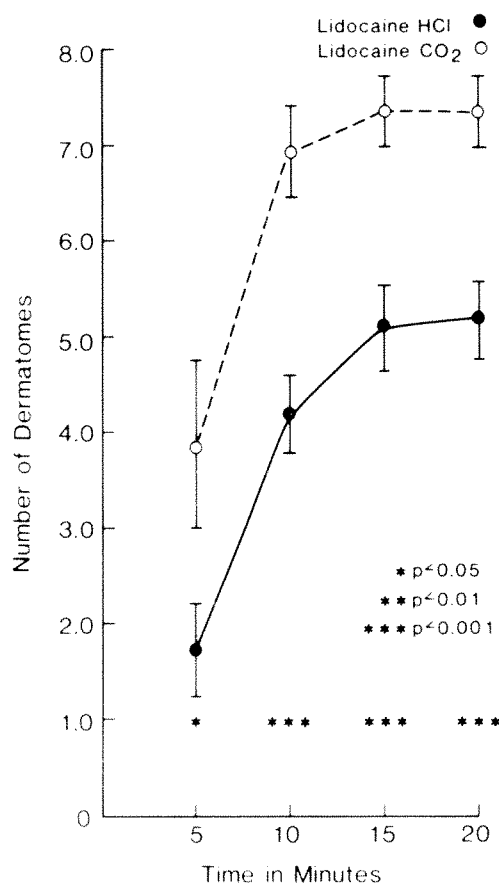
Table 4. Rapidity of Spread of Local Anesthetic

Modality	Drug	Dermatomes blocked (time to onset of sensory block in min, mean $\pm$ SDM)								
		C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈	T ₁	T ₂
Analgesia	Lidocaine-HCl	3.5	2.6	2.23	2.03	2.40	3.33	4.0	4.7	6.0
		± 2.12	± 0.81	± 0.92	± 0.48	± 0.63	± 1.95	± 2.0	± 1.89	± 2.2
	Lidocaine-CO ₂	2.4	2.18	2.0	1.8	2.0	2.53	3.06	3.33	4.78
		± 1.14	± 1.16	± 0.92	± 0.41	± 2.53	± 1.24	± 1.66	± 1.71	± 2.63
Anesthesia	Lidocaine-HCl	5.0	7.5	7.0	6.13	8.0	9.23	9.57	12.28	11.0
			± 2.88	± 3.41	± 2.06	± 2.90	± 3.00	± 3.69	± 4.53	± 1.10
	Lidocaine-CO ₂	8.6	6.27	5.2	5.4	6.33	6.66	7.66	7.61	8.16
		$\pm 6.54^a$	± 2.24	± 2.13	± 2.13	± 2.58	$\pm 2.41^a$	± 2.69	$\pm 2.69^b$	$\pm 3.86^b$

^a $P \leq 0.05$.

^b $P \leq 0.01$.

Figure 5. Graphic comparison of the number of dermatomes blocked by each agent as a function of time. The number of dermatomes blocked at each 5-min interval is greater (and the latency is shorter) with the carbonated salt, and each difference between the two agents is statistically significant as indicated.



the *rate of onset* and the *extent of spread* of a local anesthetic compared with the more traditional hydrochloride salt. The greater number of dermatomes blocked by the carbonate in the present study is evidence of the increased *extent* of spread produced by the carbonate, whereas the reduction in onset time indicates the greater *rapidity* of spread. In an earlier study (3) the authors already demonstrated that penetration of the connective tissue barriers surrounding a nerve and intraneural diffusion are also more rapid with the carbonate than with the hydrochloride salt.

From a clinical point of view, the results of the present study indicate that the interscalene technique of brachial plexus block carried out with lidocaine carbonate provides surgical anesthesia in 87% of the cases within 8–10 min from the time of injection, whereas lidocaine hydrochloride produced surgical anesthesia in only 53% of the cases; even in those patients who achieved such anesthesia, 13–17 min was required before anesthesia was complete. Lidocaine carbonate thus provides a clinically significant

reduction in latency and an increase in the spread of anesthesia. It must be remembered that in a previous study, the authors demonstrated that the duration of surgical anesthesia with lidocaine, whether hydrochloride or carbonate salt, may be too short for many surgical procedures and may thus limit the clinical usefulness of either solution. However, McClure and Scott (4) demonstrated a similar reduction in latency and increase in spread of anesthesia produced by the carbonate salt of bupivacaine compared to the hydrochloride salt, so it would appear that carbonated salts of longer-acting local anesthetics would also be clinically superior to the hydrochloride salts in common use today.

Originally, the interscalene technique of brachial plexus block was intended for upper arm and shoulder surgery. However, because of the increased extent of anesthesia provided by the carbonate salts of local anesthetics, using carbonated preparations would allow the interscalene technique to be a useful alternative to the axillary and subclavian perivascular tech-

niques of brachial block even for hand surgery. Obviously, the 38% reduction in onset time provides an additional clinically useful advantage of the carbonate salt.

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Sympathetic Blockade Increases Tactile Sensitivity

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KISSIN I, McDANAL J, BROWN PT, XAVIER AV, BRADLEY EL. Sympathetic blockade increases tactile sensitivity. *Anesth Analg* 1987;66:1251-5.

To determine whether tactile sensitivity of the normal skin is altered by suppression of sympathetic efferent activity, the effect of stellate ganglion block and epidural sympathetic block on touch threshold was studied. The study was performed on ten individuals with various chronic pain syndromes. Tactile sensitivity was measured in the normal skin area with the use of von Frey filaments and a two-alternative forced-choice procedure with a staircase presentation of touch stimuli. With stellate ganglion block, touch threshold decreased on the side of the block by $48.8 \pm 8.8\%$ ($P = 0.002$) without any significant change in the threshold on the healthy,

nonblocked side ($P = 0.003$ for the difference between the sides). With epidural sympathetic block, touch threshold decreased to the same extent on the diseased and healthy sides, which were both affected by the block ($46.2 \pm 11.4\%$, $P = 0.027$ and $47.7 \pm 12.5\%$, $P = 0.032$, respectively). The results show that sympathetic blockade increases tactile sensitivity. They also suggest that sympathetic efferent activity modulates the function of tactile receptors. It is hypothesized that the sympathetic modulation makes tactile receptors less sensitive to touch, less specific, and probably more prone to code tactile stimuli in such a way that the brain recognizes this code as pain.

Key Words: SYMPATHETIC NERVOUS SYSTEM—tactile sensitivity. SKIN—tactile threshold.

A prominent feature of the pain relieved by sympathetic blocks is the extreme sensitivity to mechanical stimulation (1,2). Because the relief of pain in causalgia and reflex sympathetic dystrophy is associated with the abolition of mechanical allodynia (painful sensation to a tactile stimulus), it seems likely that the sympathetic nervous system controls tactile sensitivity. Presently many experimental data indicate that the sympathetic nervous system modulates the function of cutaneous mechanoreceptors. Sympathetic stimulation (or application of norepinephrine) has been shown to lower the threshold of a frog's skin mechanoreceptor so much that it eventually fired spontaneously (3,4). In cats, slowly adapting type I mechanoreceptors (which are responsive to light touch) have been reported to develop a resting discharge during sympathetic stimulation (5). In experiments with the cat's hair receptors, sympathetic stimulation resulted in an increased threshold of the mechanoreceptor; however, some of these receptors demon-

strated a transient spontaneous activity (when sympathetic stimulation was present but there was no hair movement) (6). If sympathetic stimulation increases the sensitivity of the cutaneous mechanoreceptors, it seems reasonable to expect that sympathetic block might increase the tactile sensitivity of normal skin.

The aim of the present study was to determine whether sympathetic block changes tactile sensitivity of normal skin in humans.

Methods

The study protocol was approved by the Institutional Review Board. Subjects of the study were patients with various pain syndromes scheduled for stellate ganglion (cervicothoracic sympathetic) block or differential epidural (sympathetic) block. The blocks were used to determine the presence of sympathetic components contributing to the pain and to determine whether sympathetic block might be a useful treatment modality for a patient. Ten patients (three men and seven women) with ages varying from 25 to 79 yr (50 ± 21 , mean $\pm$ SD) participated in the study (Table 1). None had allodynia.

Tactile sensitivity was determined by a modification of the von Frey method (7,8). The esthesiometer set containing ten filaments of equal length, ranging

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Table 1. Characteristics of Patients

Patient No.	Age (yr) & sex	Basic diagnosis	Area of pain	Side of disease	Duration of symptoms before block
1	36M	Status post-traumatic injury	Shoulder	Right	3 yr
2	25F	Myofascial pain	Neck	Right	6 yr
3	71F	Postmastectomy pain	Upper trunk, neck, and arm	Left	12 yr
4	27M	Status post-traumatic injury	Dorsal surface of hand	Left	4 months
5	46F	Carpal tunnel syndrome	Hand	Right	8 months
6	79F	Postherpetic neuralgia	Upper back and shoulder	Right	9 months
7	64F	Status postcervical laminectomy	Shoulder and arm	Right	2 yr
8	26F	Pain after burns	Dorsal area of foot	Right	4 months
9	75F	Postherpetic neuralgia	Low back, abdomen	Right	1 month
10	48M	Cervical radiculopathy	Neck and arm	Left	1- $\frac{1}{2}$ yr

FILAMENT NUMBER	STIMULUS INTENSITY (log ₁₀ 0.1 mg)	1	1	2	2	2	1	2	2	2	1	2	RANDOM #													
		1	1	2	2	2	1	2	2	2	1	2	1	1	2	2	1	1	2	1	1	2	1	2	2	2
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
1	3.89																									
2	3.68																									
3	3.45	x																								
4	3.15		x																							
5	3.00			x																						
6	2.90				x						(x)															
7	2.70					x		(x)		0		x		(x)		(x)		(x)								
8	2.54						(0)		(0)				(0)		(0)		(0)		x		(x)					
9	2.30																			(0)						
10	1.85																									

Figure 1. Data sheet for touch threshold determination. The random numbers at the top of the figure indicate whether the touch stimulus was presented after the first or second auditory cue. X, Correct; 0, incorrect responses of a subject. Circled X and 0 represent reversal points from correct-to-incorrect or incorrect-to-correct answers. The last ten reversals were used to determine a mean value (see Methods section).

in diameter from 0.06 to 0.32 mm, was used in the study. The force required to bend each filament was calibrated and ranged from 0.007 to 0.780 g. Each filament pressure in grams was converted to log 0.1 mg. The common logarithm of the force was used in computation of thresholds. This measure was related to the serial order of the filaments (based on their diameter) in an approximately linear fashion; therefore, a scale of stimuli with roughly equal intervals resulted (Fig. 1). To measure touch threshold, a two-alternative forced-choice procedure with a staircase presentation of stimuli (7,8) was employed. A sequence of touch and no-touch stimuli was presented in a series of trials. Each period of stimulation was signaled by an auditory cue, and the touch stimulus followed either the first or second cue with a 3- to 5-sec pause between them. After both auditory cues, the subject was asked to indicate whether the stimulus occurred after the first or second cue. Presentation of a touch or a no-touch stimulus occurred either after the first or second cue according to the randomly predetermined sequence. The investigator made similar movements after each auditory cue, whether representing a stimulus or not. If an individual was not sure when a touch occurred, he was asked to guess. Trials began with a high-pressure stimulus, and its

intensity was decreased on successive trials until an incorrect choice was made. This change from a right to a wrong choice was noted as a reversal point. Trials continued until 12 reversals from correct to incorrect, or incorrect to correct, were made. Threshold was then defined as the mean of the last ten reversals; the first two reversal values were ignored (Fig. 1).

A 1-cm² area on the hairless volar surface of the forearm close to the wrist or the medial surface of the crus above the medial malleolus was used for the measurements. Because the aim of the study was to determine the block-induced changes in tactile sensitivity in the normal skin, patients who had pain in the area designated for the tactile sensitivity measurements were excluded from the study. Tactile sensitivity measurements were performed twice in the same area, 10 min before the block and 20 min after. The measurements were made on both arms (or legs). With the stellate ganglion block, the nonblocked side served as a control; with the epidural block, the diseased side and the healthy side were both affected by the sympathetic block. Temperature of the skin surface was measured before every threshold measurement with a thermister disc probe (Yellow Springs Instruments).

Stellate ganglion block was induced with 0.25%

Table 2. Individual Responses to Sympathetic Blocks

Patient No.	Type of block	Tactile threshold						Skin temperature (before → after, °C)				Horner's syndrome
		Diseased side with block		Healthy side with block		Healthy side without block		Diseased side with block	Healthy side with block	Healthy side without block		
		Baseline (mg)	Change in %	Baseline (mg)	Change in %	Baseline (mg)	Change in %					
1	SGB(R) ^a	58	-28	—	—	35	20	27.2 → 34.5	—	28.2 → 29.0	Yes	
2	SGB(R)	24	-29	—	—	13	0	34.8 → 34.8	—	35.0 → 34.2	Yes	
3	SGB(L)	24	-42	—	—	14	29	30.3 → 32.1	—	31.0 → 31.8	Yes	
4	SGB(L)	32	-47	—	—	21	-10	31.1 → 35.5	—	31.8 → 32.7	Yes	
5	SGB(R)	39	-67	—	—	12	33	29.1 → 30.5	—	29.5 → 28.7	Yes	
6	SGB(R)	152	-80	—	—	28	-14	30.1 → 31.7	—	30.9 → 31.5	Yes	
7	EB(Cer)	27	-52	40	-48	—	—	29.3 → 28.0	30.1 → 29.1	—	—	
8	EB(Lum)	29	-55	21	-19	—	—	26.0 → 26.0	26.0 → 25.5	—	—	
9	EB(Lum)	46	-65	158	-80	—	—	25.8 → 25.0	24.9 → 24.5	—	—	
10	EB(Cer)	288	-13	41	-44	—	—	32.6 → 33.5	32.8 → 34.1	—	—	

^aAbbreviations: SGB(R), right sympathetic ganglion block; SGB(L), left sympathetic ganglion block; EB(Cer), cervical epidural block; EB(Lum), lumbar epidural block.

bupivacaine (15 ml). Epidural sympathetic block (9) was performed as a component of differential epidural block: First, saline was injected, then (after 20 min) 0.5% lidocaine, and finally 2% lidocaine. Tactile sensitivity was measured 10 min before and 20 min after injection of 0.5% lidocaine. The epidural block was either lumbar (15 ml) or cervical (7 ml) depending on the pain location. With the lumbar epidural block, the catheter was introduced at the L3-L4 level and, with the cervical epidural block, at the C7-T1 level. Statistical analysis was made using a paired *t*-test and analysis of variance (10).

Results

As illustrated in Table 2, sympathetic blockade decreased touch threshold in all ten patients whether it was stellate ganglion block or epidural sympathetic block. All patients with stellate ganglion block developed Horner's syndrome. Skin temperature changes after sympathetic blockade were quite variable, from no increase to an increase of 7°C. With the epidural block, several patients had some decrease in skin temperature, probably due to long duration of the procedure and hence extended skin exposure to room air. The sympathetic blocks resulted in complete pain relief in one of our patients (Patient 2) and in pain relief of more than 50% in two other patients (Patients 1 and 7). None of the patients had a combination of symptoms typical for reflex sympathetic dystrophy (continuous burning pain, allodynia, and pain relief during sympathetic block).

Table 3 reflects average changes in touch threshold in patients with stellate ganglion block and with epidural sympathetic block. Stellate ganglion block caused a decrease of tactile threshold on the side of the block without any significant changes of the threshold on the nonblocked contralateral side. The difference between the changes in the blocked and nonblocked sides was statistically significant ($P = 0.003$). Epidural sympathetic block decreased touch threshold on both diseased and healthy sides. The degree of the decreases in touch threshold with stellate ganglion block, with epidural block on the diseased side, and with epidural block on healthy sides were almost the same: $48.8 \pm 8.5\%$ ($P = 0.002$), $46.2 \pm 11.4\%$ ($P = 0.027$), and $47.7 \pm 12.5\%$ ($P = 0.032$), respectively. With a statistical validation based on a pooled within groups error term from blocked-induced changes in touch threshold (which is admissible because of apparent homogeneity of variations in block-induced changes), *P* values for the above three groups decreased to 0.0006, 0.0027, and 0.0026, respectively.

Table 3. Effect of Sympathetic Blocks on Touch Threshold

	Changes (%) in tactile threshold after injection of local anesthetic for sympathetic blocks			
	Diseased side with block	Healthy side with block	Healthy side without block	Difference
SGB ^a (patients 1-6) ^b	-48.8 ± 8.5 ^c <i>P</i> = 0.002	—	9.7 ± 8.3 <i>P</i> = NS	-58.5 ± 10.6 <i>P</i> = 0.003
EB (patients 7-10) ^b	-46.2 ± 11.4 <i>P</i> = 0.027	-47.7 ± 12.5 <i>P</i> = 0.032	—	1.5 ± 14.4 <i>P</i> = NS

^aAbbreviations: SGB, stellate ganglion block; EB, epidural block.^bSee Table 2.^cMean ± SEM.

Discussion

Our results demonstrate an increase in tactile sensitivity caused by the sympathetic blocks. With stellate ganglion block, touch threshold decreased only on the side of the block without any significant change in tactile sensitivity on the healthy nonblocked side. With epidural sympathetic block, touch threshold also decreased, and the tactile sensitivity changes were more or less similar on the diseased and healthy sides, which were both affected by the blockade. This fact suggests that tactile sensitivity over the normal skin area on the diseased side of the body responded to sympathetic block no differently than did the normal skin over the healthy side of the body. The decrease in touch threshold after sympathetic block demonstrated in our study and hyperesthesia to touch described by several authors in patients after sympathectomy (11,12) probably have the same underlying mechanism.

When skin temperature decreases substantially below normal, there is a decrease in tactile sensitivity (13). In our study, the extent of the increase in skin temperature after the block varied from 0 to 7°C, and there was no correlation between changes in temperature and in touch threshold (Table 2). Variability in the skin temperature response agrees with the data on variability of the forearm cutaneous vessels response to sympathetic blockade; vasodilation, vasoconstriction, or no change depending on a body thermoregulatory state (14).

The change in touch threshold induced by sympathetic block confirms the view that the sympathetic nervous system modulates the function of cutaneous mechanoreceptors (3-6). Sympathetic stimulation has been shown to increase the mechanoreceptor threshold (cat's hair receptor) (6,15) or, on the contrary, decrease it (frog's skin mechanoreceptor) (3,4). Sympathetically induced changes in the mechanoreceptor response pattern to an adequate mechanical stimulus as well as spontaneous activity of the mechanorecep-

tors was described by Loewenstein (3). A resting discharge during sympathetic stimulation was demonstrated in slowly adapting type I mechanoreceptors (5). Transient mechanoreceptor excitation at the onset of sympathetic activity has been reported even with the receptors increasing their threshold to mechanical stimulation (15). It is of interest that in studies on unmyelinated polymodal nociceptors (thought to evoke sensation of burning pain), sympathetic stimulation did not affect responsiveness of these receptors (16-18). At the same time, sympathetic stimulation enhances activity in injured afferents (19,20).

The decrease of touch threshold induced by sympathetic block in normal skin demonstrated in our study and the therapeutic effect of this type of block in allodynia and hyperpathia (1,2) may be regarded as contradictory results. However, they do not seem to be conflicting within the framework of the following hypothesis. Sympathetic efferent action on cutaneous mechanoreceptors, specialized to detect touch, transforms them into less specific receptors, providing both tactile and painful sensations. These modulated receptors are less specific for touch, and therefore tactile sensitivity mediated by them is decreased. On the other hand, being low-threshold mechanoreceptors, they provide painful sensation to stimuli that have energy intensity greatly below the tissue-damaging level. How can sympathetic efferent action convert mechanoreceptors specialized to detect touch into receptors signaling pain? It is possible to suggest that the sympathetic nervous system can do it by modulating the process of coding of tactile stimuli in the mechanoreceptors. The coding theory of pain sensation opposes the view that pain is a "specific modality" with specialized sensory end organs (21,22). Presently, evidence for the concept that mammalian cutaneous receptors are specialized for nociception is prevailing (23). However, in any case it is conceivable that strong sympathetic modulation may switch nociception into a phylogenetically older, less specialized way of functioning when the same receptor is responsible for both touch and pain. For example,

sympathetic block with guanethidine (acting peripherally) has been shown to remove pain and allodynia in pain syndromes due to lesions of the brain when peripheral nerves and the skin are not damaged (24,25); if allodynia in these states is caused by increased sympathetic efferent activity, sympathetic block can reverse abnormal coding function of the mechanoreceptors and restore the normal tactile sensitivity.

In conclusion, sympathetic blockade increases tactile sensitivity in humans. This finding confirms the view that the sympathetic nervous system modulates the function of cutaneous mechanoreceptors.

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Disposition of Propofol Administered as Constant Rate Intravenous Infusions in Humans

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The disposition of the intravenous anesthetic propofol was studied when administered as a constant rate infusion at 3, 6, and 9 mg·kg⁻¹·hr⁻¹ for at least 2 hr to three groups of six patients each undergoing surgery under regional anesthesia. Arterial blood samples were collected at selected times during and up to 8 hr after infusion. Whole blood propofol concentrations were determined by high-performance liquid chromatography with fluorescence detection. Using a non-linear least-squares regression analysis, the individual data sets were best fitted by a three-compartment open mamillary model with central elimination in 17 patients. In one patient a biexponential equation was more appropriate. Derived pharmacokinetic parameters expressed as mean values ± SD indicated an initial fast distribution ($t_{1/2\beta}$; 2.8 ± 1.2 min), with an intermediate phase ($t_{1/2\alpha}$; 31.4 ± 14.7 min), and

a long terminal phase ($t_{1/2\beta}$; 355 ± 227 min), a large volume of distribution at steady state (V_{ss} ; 287 ± 213 L), and a high blood clearance (Cl_b ; 1.7 ± 0.3 L/min). The fraction of drug in the central compartment in the terminal phase was low (F_c , 0.02). The elimination rate constant (K_{10} ; 0.1190 ± 0.0351 min⁻¹) was large compared with the other transfer rate constants and was responsible for the large amount of drug eliminated during distribution. The fraction of drug eliminated during the terminal phase amounted to 0.28. The slow return of drug from remote tissues (K_{31} ; 0.0033 ± 0.0013 min⁻¹) was rate limiting in the ultimate elimination. After 120 min of infusion, $85 \pm 15\%$ of the predicted concentration at steady state (C_{ss}) was obtained; C_{ss} was linearly related to the infusion rate. The pharmacokinetic profile of propofol appeared linear over the dosage range studied.

Key Words: ANESTHETICS, INTRAVENOUS—propofol. PHARMACOKINETICS—propofol.

Propofol, 2,6-diisopropylphenol formulated in an oil in water emulsion (Diprivan, a trademark and the property of Imperial Chemical Industries PLC), is an hypnotic agent effective for the intravenous induction of anesthesia (1). Its duration of action is short, related to its rapid metabolism to inactive substances (2). Administered by intravenous infusion, propofol provided anesthesia characterised by smooth maintenance of unconsciousness devoid of excitatory problems (3). The pharmacokinetic profile of the emulsion formulation of propofol (4,5) indicated the drug was rap-

idly cleared from circulating blood but also extensively distributed in humans. Propofol total body clearance was about half that reported by Adam et al. (6) for the previous Cremophor formulation and the terminal half-life was substantially longer. This difference was probably due to the definition of a third exponential phase in the recent studies with the emulsion formulation as a result of the longer sampling period.

To predict appropriate long-term infusion regimens, it is important to determine the disposition of propofol during intravenous infusions compared to the kinetics of a single bolus administration. Clinical convenient infusion schemes, advocated to rapidly obtain and consecutively maintain therapeutic drug concentrations, are generally combinations of a bolus injection followed by an initial rapid infusion and a slower maintenance infusion. Based on the pharmacokinetic profile of the drug, the bolus injection should theoretically be followed by a bi- or triexponentially decreasing infusion rate to compensate for the initial distribution of the drug, its transfer to remote com-

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partments, and its elimination. Because proper pharmacokinetic analysis becomes very complex using such therapeutic regimens, we preferred to administer propofol as a constant rate infusion at three different rates to evaluate the linearity of the pharmacokinetics of the drug.

Material and Methods

Eighteen ASA I or II Caucasian patients with no evidence of cardiovascular, hepatic, renal, hematologic, or metabolic disorders on biological screening were scheduled for surgery under regional anaesthesia. They participated in the open study after their informed consent was obtained and were allocated to one of three groups to receive propofol at 3 ($n = 6$), 6 ($n = 6$), or 9 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ ($n = 6$) depending on the depth of anesthesia required in association with regional anesthesia (Table 1). Comparable with respect to weight and height, patients given 3 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ were, however, significantly older than those given 9 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$. Surgical procedures included transurethral resections (11), percutaneous litholapaxy (5), ureterorenoscopy (1), and resection of necrotic superficial tissues (1). All patients were premedicated with 0.4 mg glycopyrrolate IM. An intravenous infusion of dextrose 5% in lactated Ringer's solution was started in a forearm or hand vein. A radial artery was cannulated with a 20-g catheter in the contralateral arm for blood sampling. Analgesia was provided by local infiltration with 1% lidocaine (with 1:100,000 epinephrine) in six cases or by hyperbaric spinal anesthesia with either 5% lidocaine (three cases) or 0.5% bupivacaine (nine cases). The propofol infusion, connected in parallel with the intravenous infusion, was started before or after the local anesthetic block was completed based on clinical convenience and was continued for at least 2 hr (13 patients) and up to 4 hr as required by surgery. All patients breathed spontaneously throughout the procedure.

Arterial blood samples (5 ml) were taken before initiation of the propofol infusion and at 2,4,6, 8,10,20,30,40,50,60,75,90,105, and 120 min after beginning the infusion. When the infusion was continued beyond 120 min, additional samples were taken as appropriate. Further samples were taken 2,4,6, 8,10,20,40,60,90,120,180,240,300,360,420, and 480 min after the end of the infusion. All samples were collected in tubes containing potassium oxalate and, after thorough mixing, were stored at 4°C until analyzed for propofol content. Blood samples (0.5 or 1.0 ml) to which internal standard (thymol) had been added were buffered with 1 ml 0.1 M potassium dihydrogen orthophosphate and extracted with 5 ml cyclohexane.

Table 1. Population Characteristics

Characteristics	Propofol infusion rate ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$)		
	3	6	9
Females	0	2	3
Males	6	4	3
Weight (kg)	75.0 ± 7.2	65.5 ± 11.5	61.6 ± 12.5
Height (cm)	172.6 ± 2.4	163.5 ± 7.9	169.3 ± 8.8
Age ^a (yr)	60.3 ± 4.9	50.6 ± 14.7	39.8 ± 10.0

^aSignificant difference between the 3 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ group and the 9 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ group at probability level $P < 0.05$.

To an aliquot of the organic phase (4.5 ml), 0.2 M alcoholic tetramethylammonium hydroxide (50 μl) was added. The alkalized cyclohexane was evaporated to dryness at ambient temperature in a stream of nitrogen. The residue was reconstituted in high-performance liquid chromatography (HPLC) eluent (acetonitrile:water:85% orthophosphoric acid, 60:40:0.2) and an aliquot injected onto an HPLC column (100 $\times$ 5 mm ID) containing Hypersil ODS (3 μm diameter). Propofol and thymol were detected by fluorescence at 310 nm after excitation at 276 nm. Concentrations of propofol in test samples were determined by comparing the peak height ratio of propofol to thymol in test samples with those in a calibration series extracted as part of the same analytical run. The coefficient of variation of the assay was approximately 8% over the concentration range studied and the lower limit of the assay sensitivity was 4 ng/ml.

The triexponential structural model shown below, as derived by Colburn (7), was fitted to the individual propofol blood concentration data sets using the extended least-squares, curve-fitting program "Elsfit" described by Peck et al. (8):

$$C_{(T+t)} = C_1(1 - e^{-\pi \cdot T}) \cdot e^{-\pi \cdot t} + C_2(1 - e^{-\alpha \cdot T}) \cdot e^{-\alpha \cdot t} + C_3(1 - e^{-\beta \cdot T}) \cdot e^{-\beta \cdot t},$$

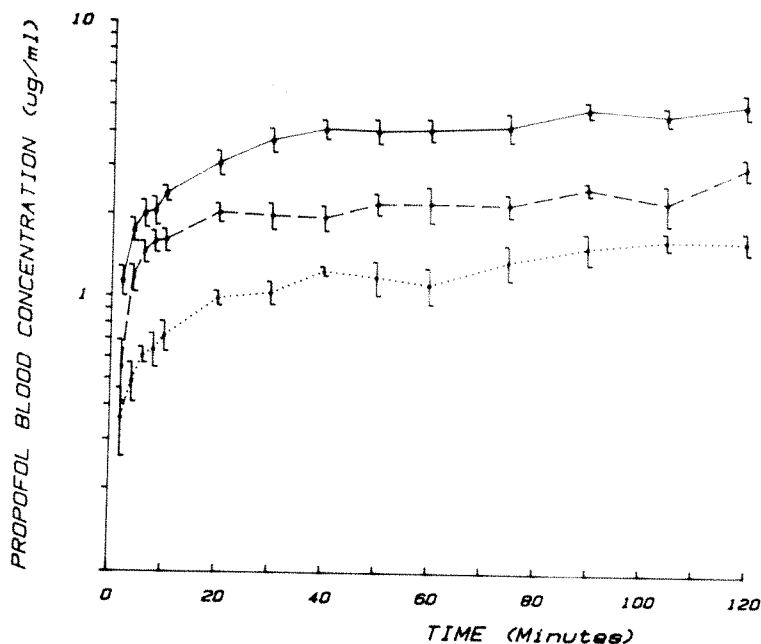
where $C_{(T+t)}$ is the propofol concentration at any time ($T+t$) after the start of the infusion. T is the infusion duration; t is the postinfusion time; and C_1 , C_2 , C_3 , π , α , and β are the three intercepts and slopes of the three exponential phases, respectively. Initial estimates for the constants were obtained using the standard feathering technique on the postinfusion data. Intercept estimates were corrected for duration of the infusion.

The fitting procedures were repeated to the biexponential structural model:

$$C_{(T+t)} = C_1(1 - e^{-\alpha \cdot T}) \cdot e^{-\alpha \cdot t} + C_2(1 - e^{-\beta \cdot T}) \cdot e^{-\beta \cdot t}.$$

The goodness of fit of the bi- and triexponential function to the data was compared using the Schwarz

Figure 1. Mean propofol blood concentration $\pm$ SEM as a function of time during propofol infusions at 3 ($\cdots$), 6 ($---$), or 9 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ ($\longrightarrow$)



criterion (9) and by visual assessment of the residuals of the individual propofol concentration values from the line of best fit.

Derived pharmacokinetic parameters including drug concentration at steady state (C_{ss}), apparent volume of distribution ($V_{d\beta}$), volume of distribution at steady state (V_{ss}), volume of the central compartment (V_c), half-lives of distribution and elimination, total blood clearance (Cl_b), and microconstants for drug transfer between compartments and for elimination were calculated from the compartmental model using standard equations (10,11).

The fraction of dose eliminated during the terminal phase was calculated as the ratio B/β (terminal macroconstant/terminal microconstant) to the total area under the concentration-time curve $[(B/\beta)/(P/\pi + A/\alpha + B/\beta)]$. Noncompartmental analysis based on statistical moments theory was performed using the trapezoidal rule (11). Mean residence time (MRT), C_{ss} , V_{dss} , and clearance were derived from the area under the concentration versus time plots to infinity (AUC) and the area under the $C_t \times t$ versus time plot to infinity (AUMC) (12). In this model, drug elimination was assumed to occur from the central compartment with first-order kinetics.

The statistical significance of observed differences between the treatment groups was assessed using the Kruskal-Wallis test. The relationships between the predicted steady-state propofol concentration and infusion rate and between the volume of distribution or clearance and the age or weight of the individual

subjects were investigated using multiple-regression analysis. All values are expressed as means $\pm$ SD.

Results

The propofol blood concentrations showed a general, but in some individuals rather erratic, increase with time during the infusion. Mean profiles were generally parallel (Fig. 1). The rate of increase gradually became slower as the steady-state concentration (C_{ss}) was approached reaching 81 ± 7 , 87 ± 6 , and $89 \pm 7\%$ of the mean C_{ss} after 2 hr of infusion in the 3, 6, and 9 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ groups, respectively. These values were not significantly different, and the overall mean was $85 \pm 15\%$. After cessation of infusion, propofol blood concentrations decayed in a curvilinear manner with time (Fig. 2). Mean profiles were also fairly parallel during the period up to 8 hr after stopping the infusion.

Individual propofol blood concentration-time data were best fitted by a triexponential function in all patients except one. Derived pharmacokinetic parameters were individually calculated assuming a three-compartment open model with central elimination in 17 patients. For one data set, obtained after a 3 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ infusion, a biexponential function was more appropriate and the derivation of pharmacokinetic parameters was amended accordingly. The half-life of the first exponential phase of this fitting has been included with the $t_{1/2\alpha}$ values. This approach has been validated by showing that the half-life value

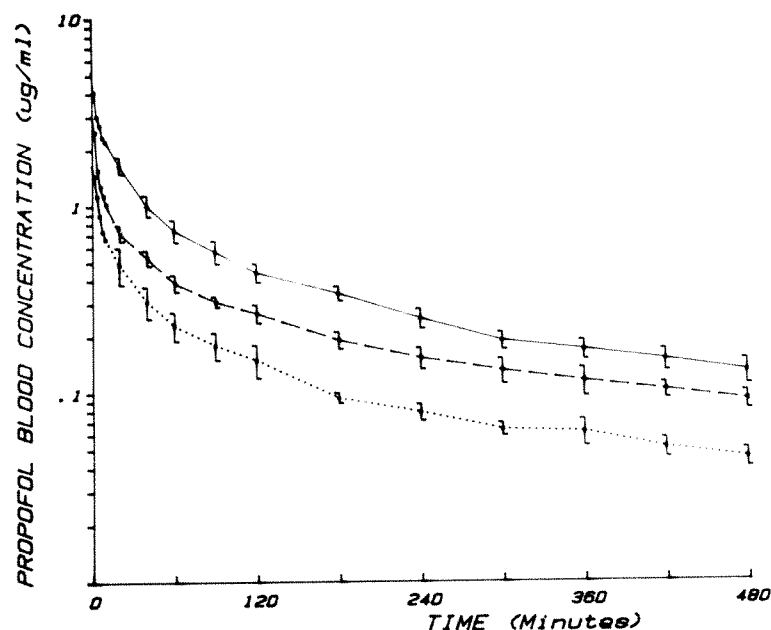


Figure 2. Mean propofol blood concentration $\pm$ SEM as a function of time after cessation of propofol infusions at 3 ($\cdots$), 6 ($---$), or 9 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ ($—$). For clarity, SEM of the first 10 min of data are omitted.

Table 2. Propofol Pharmacokinetic Parameters Derived from Compartmental (c) and from Noncompartmental (nc) Data Analysis

Parameters	Propofol rate ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$)			Mean ($n = 18$)
	3 ($n = 6$)	6 ($n = 6$)	9 ($n = 6$)	
$t_{1/2\pi}$ (c) (min)	3.1 ± 1.1^a	3.2 ± 1.1	2.3 ± 1.3	2.8 ± 1.2^c
$t_{1/2\alpha}$ (c) (min)	32.1 ± 15.2	37.5 ± 14.3	24.6 ± 14.2	31.4 ± 14.7
$t_{1/2\beta}$ (c) (min)	402.7 ± 254.4	385.5 ± 282.2	277.0 ± 138.5	355.0 ± 226.6
MRT (nc) (min)	203.6 ± 155.4	208.5 ± 199.2	117.2 ± 43.4	176.4 ± 145.6
C_{ss} (c) ($\mu\text{g}\cdot\text{ml}^{-1}$)	2.060 ± 0.432^b	3.573 ± 0.748^b	5.885 ± 0.762^b	
(nc) ($\mu\text{g}\cdot\text{ml}^{-1}$)	2.032 ± 0.450^b	3.544 ± 0.756^b	6.000 ± 0.799^b	
V_c (c) (L)	21.350 ± 9.502	16.408 ± 4.350	13.013 ± 3.633	16.924 ± 6.957
V_{ss} (c) (L)	348.333 ± 249.794	331.500 ± 256.932	181.667 ± 73.677	287.167 ± 212.855
(nc) (L)	349.167 ± 203.673	348.333 ± 257.970	175.500 ± 51.177^b	
Vd_B (c) (L)	1007.667 ± 451.195	973.333 ± 498.481	598.333 ± 244.213	859.778 ± 432.314
Cl_b (c) ($\text{L}\cdot\text{min}^{-1}$)	1.883 ± 0.414	1.864 ± 0.269	1.563 ± 0.181	1.770 ± 0.322
(nc) ($\text{L}\cdot\text{min}^{-1}$)	1.927 ± 0.512	1.892 ± 0.298	1.532 ± 0.134	1.781 ± 0.374

^aValues are expressed as mean of five values $\pm$ SD.

^bStatistical difference with the other treatment groups at probability level $P < 0.05$.

^cValues are expressed as means of 17 values $\pm$ SD.

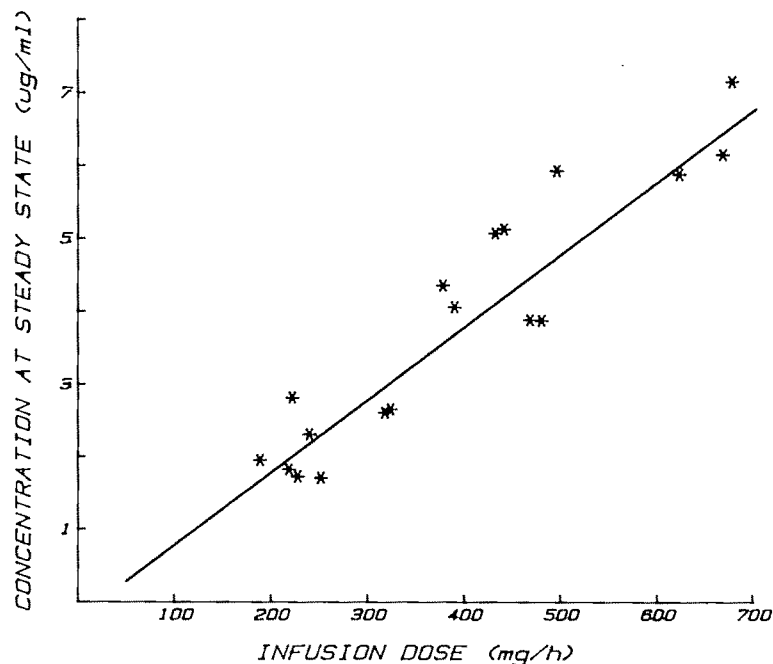
was not an outlier using the outlier test as described by Barnett and Lewis (13). Similarly, the value of V_c for this patient was not an outlier. Both of these values have therefore been included in the statistical analysis.

The results of compartmental and noncompartmental analysis were very similar and validated both methods for determination of pharmacokinetic parameters. Table 2 represents the pharmacokinetic parameters in each group and for all 18 subjects when appropriate. There were no statistically significant differences between infusion rates with respect to each of the three half-lives. Overall mean values were

2.8 ± 1.2 , 31.4 ± 14.7 , and 355.0 ± 226.6 min for the $t_{1/2\pi}$, $t_{1/2\alpha}$, and $t_{1/2\beta}$, respectively. The mean residence time (MRT) corrected for infusion duration to give a corresponding value for a bolus injection was not significantly different between the treatment groups and averaged 176.4 ± 145.6 min for the 18 subjects.

The steady-state propofol blood concentration predicted from the fitted model was shown by multiple-regression analysis to be linearly related to infusion rate expressed in milligrams per kilogram per hour and in milligrams per hour ($P < 0.001$) (Fig. 3). There was a statistically significant effect of weight ($P < 0.01$) and ponderal index defined as weight/height squared

Figure 3. Linear relationship between model predicted propofol blood concentration at steady state expressed in micrograms per milliliter and the propofol infusion rate expressed in milligrams per hour.



($P = 0.019$) on the concentration at steady state, increasing concentrations being associated with increases in both indexes.

The values of the central compartment (V_c) were appreciably higher than blood volume and were similar in the three groups with a mean value of 16.9 ± 6.9 L. The volume of distribution at steady state (V_{ss}) derived from the fitted model amounted to 287.2 ± 212.8 L. V_{ss} was approximately one-third of the corresponding apparent volume of distribution ($V_{d\beta}$), which averaged 859.8 ± 432.3 L. Both values were appreciably higher than the total body water volume, confirming the extensive distribution of propofol from blood into tissues. When calculated using the model independent method, V_{ss} was significantly lower in the $9 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ group (175.5 ± 51.2 L) when compared with the $3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ group (349.2 ± 203.7 L, $P = 0.03$) and also when compared with the $6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ group (348.3 ± 258.0 L, $P = 0.04$). However, these differences could not be confirmed when the values derived from compartmental analysis were used for statistical analysis or when body weight normalized data were compared. Multiple-regression analysis did not demonstrate any relation between the volumes of distribution and age or weight of the subjects.

The mean values of total body clearance (Cl_b) of 1.927 ± 0.512 and 1.892 ± 0.298 L/min in the 3 and $6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ groups, respectively, were higher than the value seen in the $9 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ group, which averaged 1.532 ± 0.134 L/min. However, none of these

differences were statistically significant. The individual values of clearance did not correlate with age or weight. The overall mean Cl_b was 1.781 ± 0.374 L/min.

The transfer rate constants between compartments were similar in the three groups and are summarized in Table 3. The elimination rate constant (K_{10}) amounted to $0.1190 \pm 0.0351 \text{ min}^{-1}$ and considerably exceeded the exit rate constants K_{21} , which averaged $0.0550 \pm 0.0558 \text{ min}^{-1}$, and K_{31} , which averaged $0.0033 \pm 0.0013 \text{ min}^{-1}$. In the terminal phase the fraction of drug in the body that was in the central compartment (F_c) and thus available for biotransformation was not different in the three groups and was very low (0.0204 ± 0.0077). The fraction of dose eliminated during the terminal phase averaged 0.28 ± 0.07 .

Discussion

In general our results are in good agreement with pharmacokinetic data previously reported (4,5) after the bolus injection of $2.5 \text{ mg}\cdot\text{kg}^{-1}$ propofol. The constant rate propofol infusions of 3, 6, and $9 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ resulted in the expected gradual increase in propofol blood concentrations over the period of administration. The profiles for the three infusion rates were generally parallel both during and after infusion. This parallelism, taken together with the confirmed linear relationship between C_{ss} and dose, demonstrated that the pharmacokinetics of propofol were linear over the range of infusion rates studied. The consequence of any changes in infusion rate within this range, in

Table 3. Propofol Transfer Rate Constants between Compartments Assuming a Three-Compartment Open Model with Central Elimination

Rate constants	Propofol rate ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$)			
	3 ($n = 5$)	6 ($n = 6$)	9 ($n = 6$)	Mean ($n = 17$)
K_{10} (min^{-1})	0.0966 ± 0.0292^a	0.1212 ± 0.0359	0.1288 ± 0.0431	0.1190 ± 0.0351
K_{12} (min^{-1})	0.0961 ± 0.0909	0.0696 ± 0.0465	0.1733 ± 0.1404	0.1140 ± 0.1051
K_{13} (min^{-1})	0.0380 ± 0.0075	0.0455 ± 0.0196	0.0415 ± 0.0177	0.0419 ± 0.0155
K_{21} (min^{-1})	0.0375 ± 0.0257	0.0330 ± 0.0216	0.0915 ± 0.0806	0.0550 ± 0.0558
K_{31} (min^{-1})	0.0027 ± 0.0012	0.0032 ± 0.0012	0.0039 ± 0.0014	0.0033 ± 0.0013
Fraction of drug in the central compartment during terminal phase				
F_c	0.0189 ± 0.0088	0.0190 ± 0.0070	0.0232 ± 0.0082	0.0204 ± 0.0077
Fraction of drug eliminated during the terminal phase				
	($n = 6$)	($n = 6$)	($n = 6$)	($n = 18$)
F_{el}	0.297 ± 0.069	0.298 ± 0.087	0.265 ± 0.070	0.286 ± 0.073

^aValues are expressed as mean $\pm$ SD.

terms of the resultant propofol blood concentrations, is therefore predictable on the basis of the superposition principle.

The significant effect of weight and ponderal index on the concentration at steady state in this study suggest that dosing on an absolute rather than on a body weight basis might be preferred. Similarly, Redfern et al. (14) found that the total propofol dose required to induce anesthesia did not correlate with the weight of the patient. However, in our study the increase in C_{ss} was appreciably less than proportional to body weight, this suggesting that a combination of a fixed dose and a body weight-related dose might be preferable.

The pharmacokinetic profile was best fitted by a three-compartment open model with central elimination. The three exponential phases comprised an initial very rapid distribution with a half-life of 2.8 ± 1.2 min, an intermediate phase with a half-life of 31.4 ± 14.7 min, and a terminal phase with a half-life of 355 ± 227 min.

Propofol is highly lipophilic and would be expected to cross all cell membranes easily and rapidly. The rate-limiting step in distribution is thus probably related to tissue perfusion. The initial volume of distribution (V_d) was greater than blood volume. Propofol is avidly bound to plasma proteins (98%), which suggests that the central volume of distribution of the unbound drug (V_{cu}) was about 50 times larger as $V_c = V_{cu}$ times the fraction of drug that is unbound ($f_u = 0.02$). Extensive binding to tissue components was expected and was confirmed by the high value for the volume of distribution at steady state (V_{ss} , 287 ± 213 L), which greatly exceeded body volume.

The V_{ss} value calculated using the noncompartmental analysis of the individual data was significantly

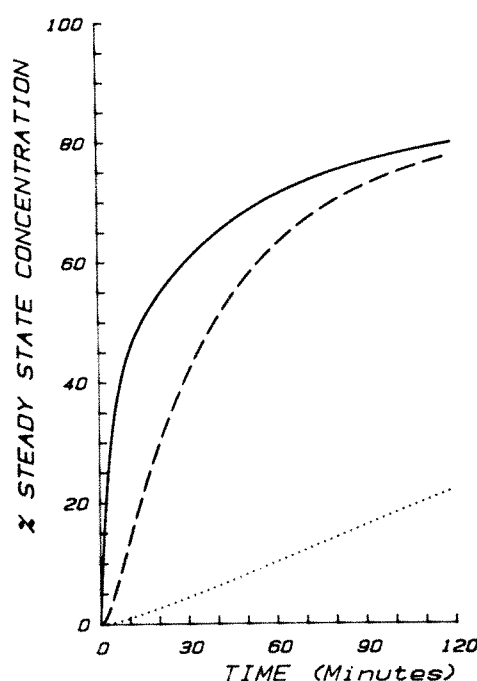


Figure 4. Percent of steady-state propofol concentration in the central compartment (—), in the second compartment (---), and in the deep compartment (·····) during an infusion of propofol for 120 min (computer simulation based on the mean pharmacokinetic parameters of 17 subjects).

cantly lower in subjects given $9 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ than in those given 3 or $6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$. This trend might indicate saturation of tissue binding, in which case the elimination rate would be increased while clearance would remain unchanged (15). Indeed a more rapid elimination was observed at an infusion rate of $9 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ but did not reach statistical significance. Clearance data suggest lower values with higher

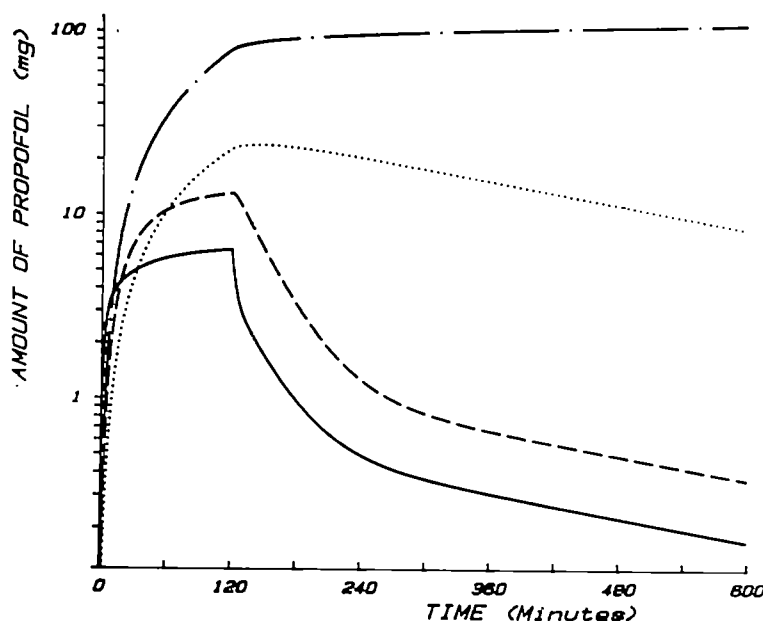


Figure 5. Amount of drug in the central compartment (—), in the second compartment (---), in the deep compartment (·····) and amount of drug eliminated (-·-·-) during and up to 8 hr after an infusion of propofol for 120 min at a rate of 1 mg/min (computer simulation based on the mean pharmacokinetic parameters of 17 subjects).

infusion rates, although the observed changes were not statistically significant. Because of the mathematical interrelationship between volume of distribution, clearance and elimination rate ($Cl = V \times \beta$), any definite interpretation at this point seems hazardous. When V_{ss} and clearance were normalized for body weight, no effect of infusion rate could be demonstrated. Body weight did not correlate with any of the pharmacokinetic parameters, and the body weight normalized data showed much more interindividual variability. Therefore, it is not surprising that those data did not exhibit statistically significant differences anymore.

Interindividual variability of the derived pharmacokinetic parameters in the $9 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ group was appreciably less than in the other two groups, whereas demographically, subjects given $9 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ were as heterogeneous as those given $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ but less homogeneous than those in the $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ group.

The apparent volume of distribution was approximately three times greater than the corresponding volume of distribution at steady state. This observation is consistent with the relatively rapid elimination of most of the administered drug during distribution and the persistence of a small fraction of drug in the central compartment in the postdistribution phase ($F_c = 0.02$) giving rise to an unexpected long terminal phase half-life. It is probable, therefore, that the elimination rate of propofol during this final phase is constrained by slow return from the deep compartment.

The high overall mean clearance value observed in

this study ($1.77 \pm 0.32 \text{ L/min}$) exceeded the generally accepted estimate for liver blood flow (1.5 L/min). Extrahepatic biotransformation sites might be postulated. Propofol is metabolized by glucuronide conjugation and by oxidation followed by the formation of glucuronide and sulfate conjugates (2). Other similarly metabolized drugs also have unusually high total body clearances in animals and humans: Mulder et al. (16) showed in the rat that extrahepatic clearance of harmol constituted about 77% of its total body clearance, and Gepts et al. (17) demonstrated a similar high clearance of meptazinol in humans. Studies with phenol (18,19) and with naphthol (20) in rats have demonstrated appreciable pulmonary metabolism. The data of Cassidy and Houston (19) also indicated that, after an intravenous bolus dose of 4.5 mg/kg and above, the pulmonary metabolic capacity appeared to be saturated.

The respective values of the transfer rate constants may be interpreted in terms of probabilities (21). Once the drug molecule enters the central compartment, its probability of being eliminated is as high as that of being transferred to the second compartment (40%) and twice as high as that of being transferred to the third compartment (20%). This clearly indicates that a great deal of elimination occurs during distribution and is consistent with the fraction of dose eliminated during the terminal phase (0.28) calculated by area proportionalities. Because K_{10} is large compared with the other transfer rate constants, equilibrium will be obtained much faster in blood than in remote tissues (Fig. 4). Fifty percent of C_{ss} is achieved in blood after

14 min of infusion while, at that moment, in the second compartment 21% of steady state and in the deep compartment only 2% of steady state are obtained. After 120 min of infusion, 22% of the equilibrium capacity of the deep compartment is achieved.

The decay in propofol blood concentration after stopping the infusion remains polyexponential in profile because drug is initially always rapidly removed from blood and redistributed. The decline in blood propofol concentrations from a therapeutic level to a level at which the patient is likely to awake (22) thus will be dominated by the redistribution and elimination during the intermediate phase, ensuring rapid recovery. The ultimate elimination is influenced by the slow movement of drug from the deep tissue compartment (Fig. 5). This last step is rate-limiting and responsible for the long terminal half-life.

We conclude that the pharmacokinetic profile of propofol administered as a constant rate infusion confirms that the drug is extensively distributed and rapidly cleared from the body. The prediction of drug levels and recovery after short-term infusions are not appreciably affected by the relatively slow equilibrating deep compartment. However, with infusions lasting several hours or days, the three-compartment model more accurately predicts the approach to steady-state blood concentrations. The third phase will not, however, play any significant part in the rate of recovery of consciousness when propofol is used in clinical anesthesia practice.

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A New Parascalene Approach to the Brachial Plexus in Children: Comparison with the Supraclavicular Approach

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DALENS B, VANNEUVILLE G, TANGUY A. A new parascalene approach to the brachial plexus in children: comparison with the supraclavicular approach. *Anesth Analg* 1987;66:1264-71.

A technique for blocking the brachial plexus was designed after reevaluation of the gross anatomy of the neck in children. It consists of penetrating the perineural sheath at the level of the omohyoid muscle using a strictly anterior-posterior direction for insertion of the needle. This procedure was prospectively evaluated in 60 children (group P) and

compared with classical supraclavicular approach in 60 similar patients (group S). Insulated needles and a nerve stimulator were used with both techniques. Although both techniques produced a high degree of sensory blockade in almost all infraclavicular branches of the brachial plexus, the parascalene approach proved to be easier and more reliable while also being almost free of complications.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—brachial plexus. ANESTHESIA—pediatric.

Regional anesthesia, especially spinal and epidural, is gaining more general acceptance in pediatrics (1-3). Peripheral blocks, however, remain rather unusual for nonemergency procedures because of either lack of reliability or the danger of complications. The supraclavicular approach to the brachial plexus (4), one of the more consistently successful methods of blocking peripheral nerves, has partially fallen into disfavor because of hazards of pneumothorax (1,5). Thus, the axillary approach to the brachial plexus is usually preferred today. The technique is easy because paresthesias are not required and undesirable effects are scarce, being mainly represented by intravascular penetration (axillary artery). Unfortunately, this approach is not suitable in several circumstances. Abducting the arm by 90° may be painful and even dangerous in traumatic lesions of the upper extremities (fractures, wounds). Moreover, anesthesia may be incomplete, especially in the area supplied by the radial nerve (6).

Winnie (7) has developed another technique, known as the interscalene approach to the brachial plexus. This technique avoids the risk of pneumothorax, but it may produce complications as severe as vertebral artery puncture and injection into the epidural or subarachnoid space of subsequent high levels of epidural

or spinal anesthesia (1,5). Also, incomplete anesthesia of the extremity with undesirable block of the phrenic or recurrent laryngeal nerves and development of Horner's syndrome are not unusual. Other approaches to the brachial plexus have also been reported (8-10), but none are free of complications and none has gained general acceptance in treating children.

We reevaluated the gross anatomy of the lateral part of the neck in infants and children with the aim of finding a pathway for insertion of the needle during block of the brachial plexus that avoids major structures in the neck. A new approach was then developed on an anatomical basis. The present study prospectively evaluates the efficacy and reliability of the modified technique and compares it with the supraclavicular approach (4). To reduce interindividual factors, all blocks were performed by the same anesthetist, while evaluation of sensory blockade and side effects was ensured by the same surgeon, who was unaware of which technique or anesthetics used. The study protocol received institutional approval.

Anatomy

The brachial plexus is enclosed in the interscalene space, between the anterior and middle scalene muscles, from the emergence of its roots from their grooved transverse process (medially and rostrally) to the point at which its trunks pass behind the clavicle (laterally and caudally) to reach the axilla. This space has a

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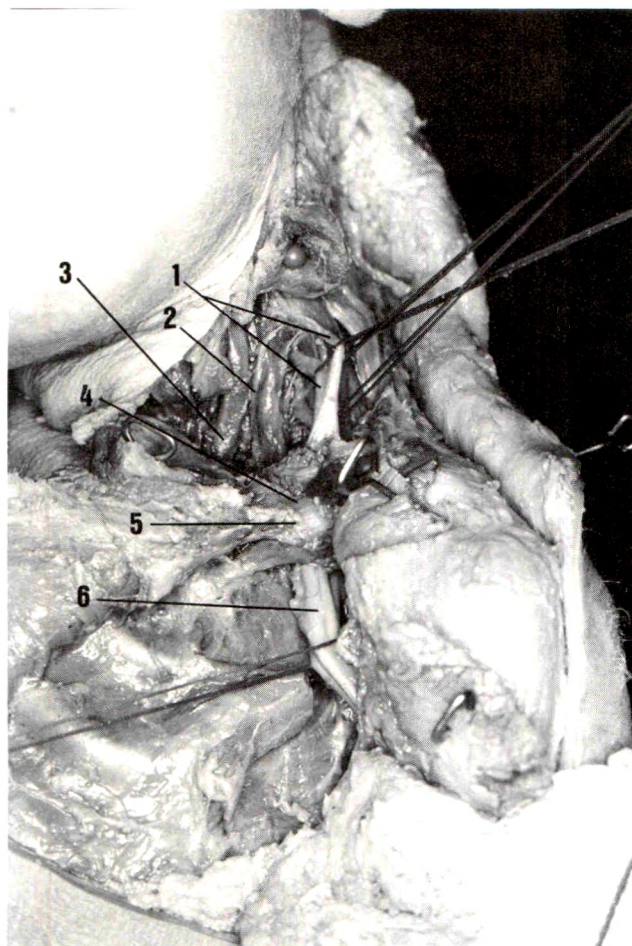


Figure 1. Dissection of the lateral part of the neck (1-month-old child). Note the continuous perineural sheath from supraclavicular to infraclavicular parts of the brachial plexus. 1) Roots of the brachial plexus; 2) phrenic nerve; 3) subclavian vessels; 4) internal jugular vein; 5) clavicle; 6) infraclavicular part of the brachial plexus.

triangular shape with three sides and two aspects. The medial side is limited by transverse processes from the C4 to C7 vertebrae: it is in relation (Fig. 1) with the great vessels of the neck, the vagus, phrenic, and laryngeal recurrent nerves, the vertebral artery, intervertebral foramina and, at its lower extremity, the stellate ganglion.

The caudal side extends from the transverse process of C7 to approximately the midpoint of the clavicle. This side lies on the first rib, the cupola of the lung and the subclavian vessels. The lateral side is formed by the skin covering the interscalene groove and is crossed by the external jugular vein. The anteromedial and posterolateral aspects are covered only by muscles and are free of vital structures.

An approach to the brachial plexus would, therefore, be safe if the needle were inserted so it pointed to neither the medial nor the caudal side of the in-

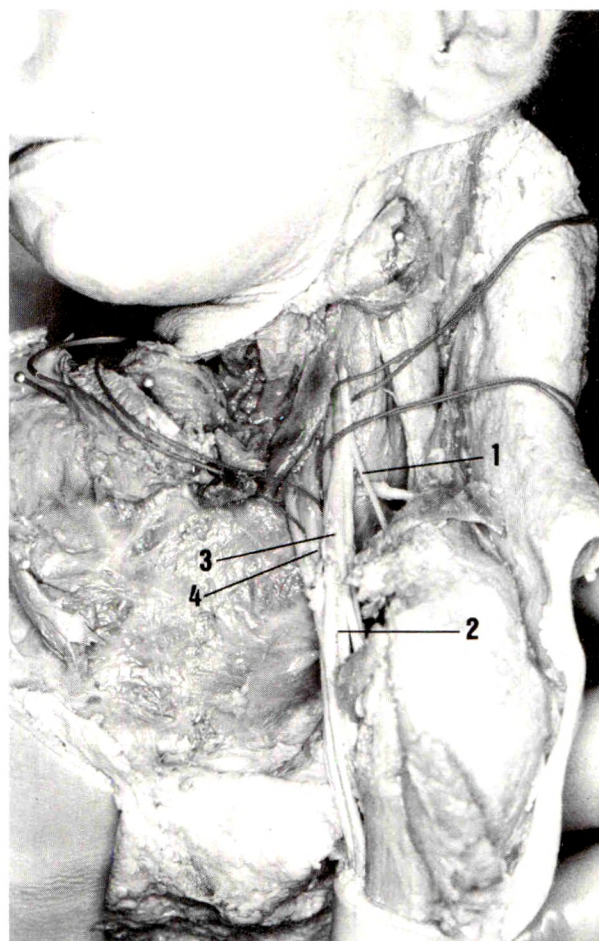


Figure 2. Same dissection as in Figure 1 after removal of the clavicle. The perineural sheath of the infraclavicular part of the BP and the fascial compartment of the supraclavicular nerve (supraclavicular part of the BP) have been dissected: note that the remaining supraclavicular branches are still completely ensheathed. 1) Suprascapular nerve; 2) infraclavicular part of the brachial plexus after complete dissection of the perineural sheath; 3) supraclavicular part of the brachial plexus (still ensheathed); 4) subclavian artery.

terscalene space. With a strictly anteroposterior insertion, the needle will only encounter muscular masses (sternocleidomastoid and anterior scalene muscles) before penetrating the interscalene space. Penetration of the needle beyond the posterior aspect of the interscalene space would only involve entry of the needle into muscles, especially middle scalene and trapezius muscles.

Within the interscalene space, the brachial plexus nerves are invested by the fascia of the anterior and middle scalene muscles, which constitute a continuous perineural sheath (Fig. 1), as described by Winnie et al. (8,11). However, the enclosed perineural space is multicompartmented with a fascial compartment for each nerve (12). In Figure 2, the trunks of the plexus remain close together and completely en-

Figure 3. Spread of 0.75 ml/kg of a solution of local anesthetics with the addition of contrast material administered via the parascalene route (radiographic findings from a 3-yr-old child not included in this study).

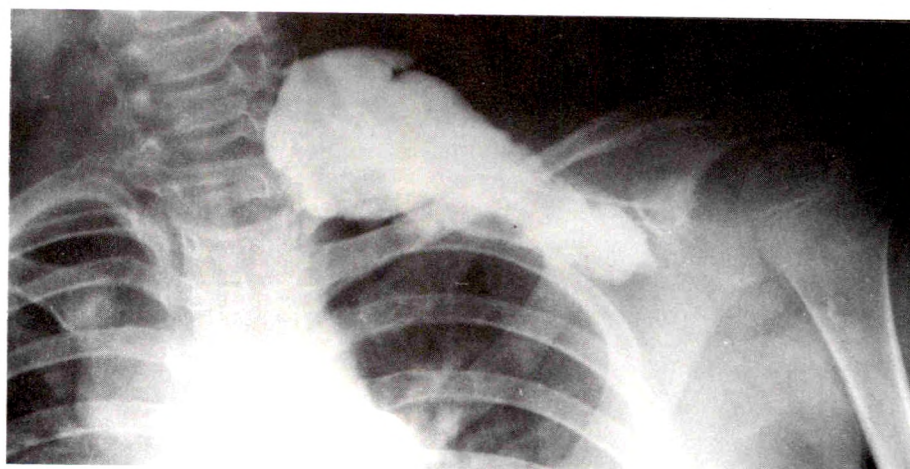


Table 1. Surgical Indications in the Two Groups (Supraclavicular and Parascalene Approaches)

Indications	Group S (n = 60)	Group P (n = 60)
Emergency procedures	41	36
Fractured humerus	6	4
Elbow dislocation	6	5
Fractured forearm	11	11
Infections (whitlows)	7	3
Wounds	10	12
Burns	1	1
Scheduled procedures	19	24
Removal of implants	11	14
Skin grafts	2	2
Malformations of fingers	3	2
Excision of tumors	2	2
Osteotomies	1	3
Arteriovenous fistula	0	1

sheathed while the fascial compartment of the suprascapular nerve has been dissected. Also, the perineural space is limited caudally, approximately at the level of the coracoid process where the nerves enter the intermuscular septum (Fig. 3). This prevents the spread of anesthetic solutions toward the axilla.

The compartmentation within the perineural sheath is incomplete at the lower part of the interscalene space where the trunks unite, as it is at the upper part of the axilla, where the brachial plexus gives off its terminal branches (median, radial, and ulnar nerves) (13). Thus, efficacy of supraclavicular blocks would be improved by the deposition of local anesthetics as closely as possible to the part where the trunks unite and where the compartmentalization is incomplete. This is best achieved at the lower part of the interscalene space, immediately above the clavicle, but danger of penetration of the cupola of the lung is considerable. Deposition of anesthetics above the up-

per edge of the omohyoid muscle would ensure that any vital structure in relation with the caudal limit of this space is not threatened. It was expected that the caudal limitation of spread of anesthetic solutions at the level of the coracoid process would facilitate diffusion of local anesthetics in the opposite direction, reaching fascial compartments that were not reached by the tip of the needle block. This clinical study was carried out to evaluate efficacy and ease of this technique using a strictly A-P approach, which we termed the parascalene approach, and to compare this with the supraclavicular approach which is generally considered the approach that results in the most effective anesthesia.

Materials and Methods

One hundred-twenty children were included in the study after informed consent from parents and, as often as possible, from children, was obtained. The children were randomly classified into two equal groups. The classical supraclavicular approach to the brachial plexus was performed in group S (supraclavicular), whereas the parascalene technique was used in group P (parascalene).

Group S comprised 44 boys and 16 girls, ranging in age from 12 months to 17 yr and in weight from 9 to 71 kg. Group P comprised 41 boys and 19 girls, ranging in age from 8 months to 17 yr and in weight from 8 to 69 kg. The indications for surgery are shown in Table 1.

Twenty-one patients in group S and 19 in group P were kept alert for both anesthetic and surgical procedures (emergency procedures in patients with a full stomach or nonacceptance of general anesthesia by the parents). The remaining patients in both groups were given general anesthesia.

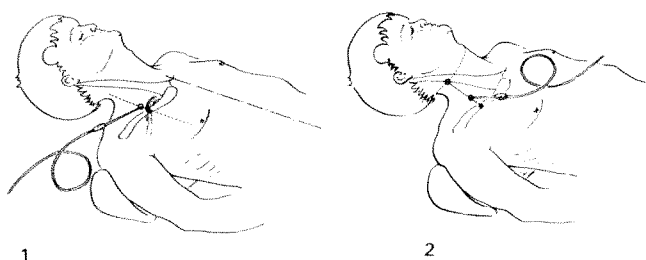


Figure 4. Landmarks and site of puncture of parascapular and supraclavicular approaches to the brachial plexus. (1) Supraclavicular approach; (2) parascapular approach.

Parascapular Approach

Position. The child is placed supine in the dorsal recumbent position with a rolled towel slipped under the shoulders and the arm extended along the chest wall with the head turned to the opposite side.

Landmarks. The landmarks are 1) the midpoint of the clavicle, 2) the posterior edge of the sternocleidomastoid muscle (SCM), and 3) Chassaignac's tubercle (transverse process of C6), located either by palpation or by drawing a sagittal line from the cricoid to the posterior edge of the SCM (Fig. 4).

A line is drawn from the midpoint of the clavicle to Chassaignac's tubercle. The site of puncture lies at the junction of the lower and the two upper thirds of this line.

Procedure. An insulated needle block connected to a nerve stimulator is inserted at 90° to the skin and is advanced in the anteroposterior plane until twitches are elicited in the upper limb (Fig. 5). The anesthetic solution is then injected at this level after aspiration and injection of a test dose. If the nerves are not located at the first attempt, the needle is withdrawn and redirected slightly laterally.

Supraclavicular Approach after Kulenkampff (4)

Position. The same position as for parascapular approach is used.

Landmarks. The landmarks are 1) the midpoint of the clavicle, 2) a line drawn from this point toward the mastoid process, parallel to the major axis of the body and, 3) the skin projection of the subclavian artery (Fig. 4). The site of puncture lies at the junction of the line with the projection of the artery.

Procedure. The same devices are used. The needle is inserted posteriorly to the subclavian artery, at approximately 40° angle medially, caudally and dorsally,

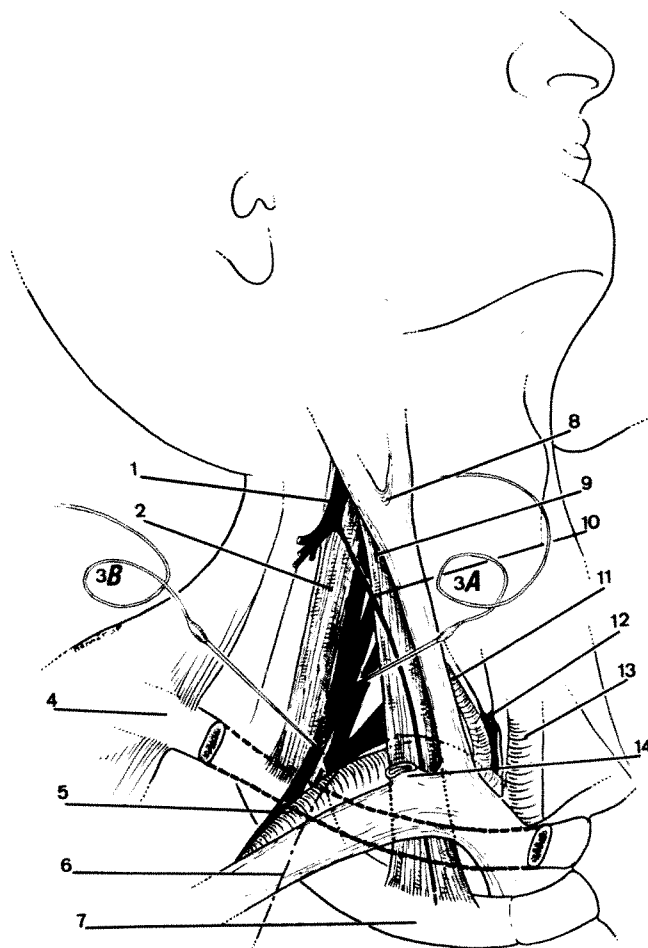


Figure 5. Insertion route used in parascapular (A) and supraclavicular (B) approaches. 1) Cervical plexus; 2) Posterior scalene; 3) Block needle; 4) Clavicle; 5) Subclavian artery; 6) Cupola of the lung; 7) First rib; 8) Internal jugular vein; 9) Anterior scalene muscle; 10) Phrenic nerve; 11) Vertebral artery; 12) Stellate ganglion; 13) Common carotid artery; 14) External jugular vein.

until eliciting twitches in the upper extremity (Fig. 5). The extreme safety limit is represented, both dorsally and caudally, by the upper limit of the first rib (which must not be overlapped).

Anesthetic Methods

All procedures were carried out in operating rooms after insertion of a catheter. Children having general anesthesia were given 0.02 mg/kg atropine and 0.05 to 0.1 mg/kg diazepam IV, anesthesia then being induced using either inhalation (halothane in 65/35% N₂O/O₂) or intravenous (4 mg/kg ketamine or pentobarbitone) agents as preferred by the children. Anesthesia was maintained using 0.25 to 0.5 halothane in 65/35% N₂O/O₂.

We used 30-mm 22-gauge insulated needles (Top

Table 2. Evaluation of the Efficacy of the Two Procedures

	Group S		Group P	
	n	%	n	%
Location of trunks	60	100	60	100
on First attempt	46	77	53	88
on Second attempt	8	13	7	12
Over two attempts	6	10	0	—
Anesthesia at site of surgery				
Complete	53	88	58	97
Incomplete	7	12	2	3
Absent	0	—	0	—
Motor blockade	32	53	36	60
Lid. ^a	9/19	47	8/15	53
Lid. + Bupi. ^b	18/29	62	16/31	52
Bupi. + Eti. ^c	11/12	92	12/14	86
Sensory blockade (mean $\pm$ SD)				
Lid. ^a	136 $\pm$ 46 min		155 $\pm$ 65 min	
Lid. + Bupi. ^b	367 $\pm$ 105 min		344 $\pm$ 83 min	
Bupi. + Eti. ^c	415 $\pm$ 130 min		442 $\pm$ 111 min	

Abbreviations: Lid., lidocaine; Bupi., bupivacaine; Eti., etidocaine.

^a1% Lidocaine with 1:200,000 epinephrine.

^b1% Lidocaine + 0.5% bupivacaine, both with 1:200,000 epinephrine.

^c0.5% Bupivacaine (with 1:200,000 epinephrine) + 1% etidocaine (without epinephrine).

needles) and a nerve stimulator (Myotest from Datex) adjusted to deliver 85 mV impulses every second. The skin was cleaned and, in alert children, anesthetized with 1–2 ml 0.5% lidocaine without epinephrine. After the needle was in the proper position and aspiration ensured that the tip was not in a vessel, a test dose (0.5 to 1 ml) was administered. The appropriate volume of anesthetic mixture (see later) was then injected over 30 to 60 seconds. The needle was then withdrawn after a mark had been made for measuring the depth to which it was inserted.

Three anesthetic solutions were selected according to the expected duration of surgery, the necessity for motor blockade, and the need for postoperative analgesia:

- 1% Lidocaine with 1:200,000 epinephrine (short duration procedures),
- A mixture of equal volumes of 0.5% bupivacaine and 1% lidocaine, both with 1:200,000 epinephrine (long duration of postoperative pain relief needed), or
- A mixture of equal volumes of 0.5% bupivacaine with epinephrine and 1% etidocaine without epinephrine (long duration of pain relief and motor blockade needed).

These solutions were administered on a weight-basis: 0.75 ml/kg up to 20 kg; 20 ml from 20 to 30 kg; 25 ml from 30 to 55 kg; and 30 ml over 55 kg.

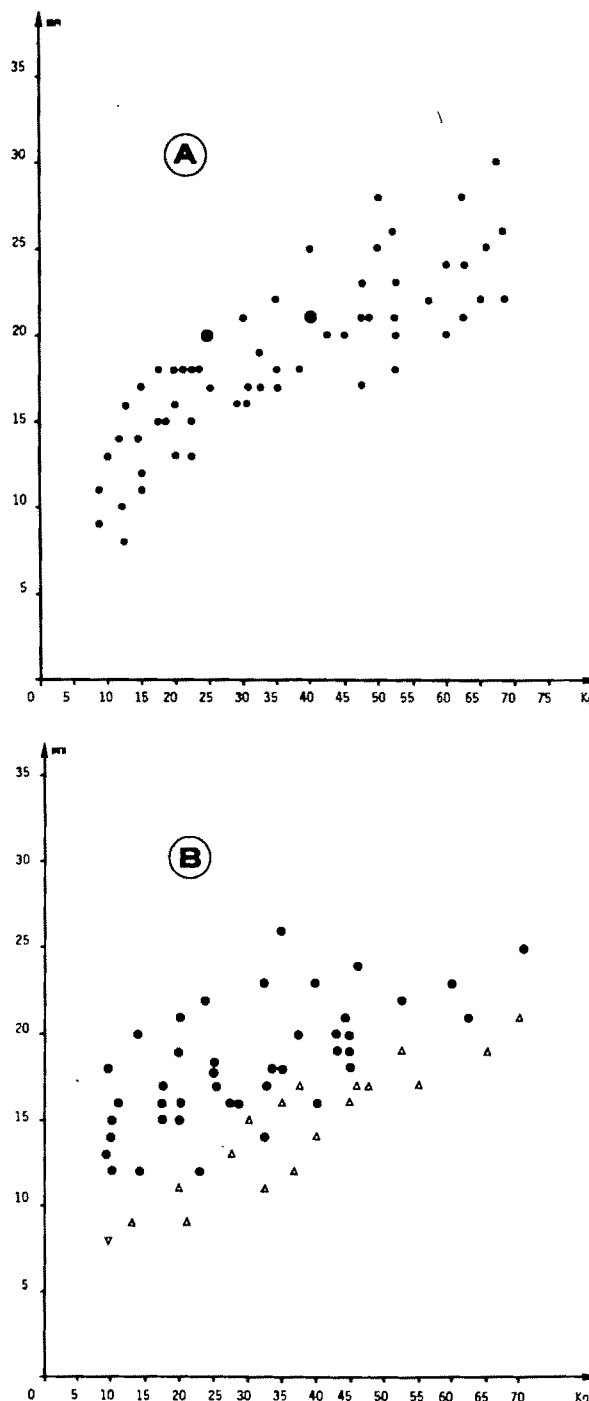


Figure 6. Depth to which the tip of the needle was inserted in relation to the weight of children. (A) Group P (large circles, Horner's syndrome present); (B) Group S (black circles, Horner's syndrome present).

Monitoring Procedures

ECG tracings were continuously monitored while respiratory rate and blood pressure (Dinamap) were measured every 3 minutes. Tidal volume, end-tidal

Table 3. Extent of Sensory Blockade in Patients with Complete Sensory Blockade at the Site of Surgery

Distribution of anesthesia	Group S (n = 53)		Group P (n = 58)	
	n	%	n	%
Lower branches of the cervical plexus	9	17	37 ^b	64 ^b
Skin of the axilla ^a	3	6	2	3
Axillary nerve	49	92	54	93
Medial antibrachial nerve	52	98	56	97
Musculocutaneous nerve	51	96	57	98
Radial nerve	51	96	55	95
Median nerve	53	100	58	100
Ulnar nerve	52	98	57	98

^aThe area in the axilla supplied by the intercostobrachial nerve (a branch from T2 spinal nerve) could not be distinguished from that supplied by the medial brachial cutaneous nerve (a branch from the brachial plexus).

^bStatistically significant difference.

CO₂, and halothane concentrations were continuously monitored in patients under general anesthesia.

After completion of surgery, sensory (skin pinching) and motor (verbal request and nociception) functions were evaluated by the (same) surgeon who was unaware of the technique chosen. The anesthetic procedures were considered successful when the operation could be completed on a motionless patient without any additional treatment. The success rate was defined as the percentage of successful procedures.

Analgesia was considered complete when no reaction (anesthetized patient) or complaint of pain (un-anesthetized patients) were observed while pinching skin areas supplied by brachial plexus nerves. It was considered incomplete when the child either complained of pain or had reactions that were not observed after pinching adjacent anesthetized areas.

Duration of sensory blockade was measured as the time from injection of local anesthetics to the complaints of pain, either spontaneously or after skin pinching (evaluated every half-hour postoperatively).

Statistical Methods

Results, expressed as mean $\pm$ SD, were analyzed using both parametric (Student's *t*-test) and nonparametric (Mann-Whitney test) tests. Qualitative parameters were evaluated using χ^2 test. Differences were considered statistically significant when $P < 0.05$.

Results

Patients from the two groups did not significantly differ in regard to age, weight, indications, and sex. There was the same predominance of 2:1 males in both groups.

Table 4. Complications

Adverse effects	Group S		Group P	
	n	%	n	%
Puncture of vessels	6	10	1	2 ^a
Subclavian artery	3	5	0	—
Subclavian vein	2	3	0	—
Unidentified small vein	1	2	1	2
Pneumothorax ^b	0	—	0	—
Phrenic nerve palsy	1	2	0	—
Horner's syndrome	42	70	2	3 ^a

^aStatistically significant difference.

^bClinical evaluation.

In all patients, the trunks of the brachial plexus were located by eliciting twitches in muscles of the upper extremity. This was achieved on the first attempt in 77% in group S and in 88% ($P < 0.05$) in group P (Table 2). The depth at which twitches were elicited is shown in Figure 6. Alert patients did not feel paresthesias and none complained of the electrical stimuli. In all cases, the twitches disappeared after <1.5 ml of anesthetic solution had been injected. A surgical level of analgesia was obtained within 12 min in all patients. Analgesia was complete in 88 and in 97% of patients in groups S and P, respectively.

The duration of pain relief was similar (Table 2) in both groups when the same anesthetic solution was used. The extent of sensory blockade (Table 3) did not significantly differ in areas supplied by branches of the brachial plexus, whereas the parascapular approach provided significantly more extensive blockade in areas supplied by the lower branches of the cervical plexus.

Complications are shown in Table 4. Two statistically significant differences were observed between groups S and P. Puncture of subclavian vessels occurred five times in group S and not at all in group P. Horner's syndrome occurred in 42 patients in group S and in only 2 in group P. Also, three patients in group S and two in group P had nausea and vomiting postoperatively. All of these patients had been anesthetized with intravenous ketamine.

Discussion

Results in group S confirm the effectiveness of supraclavicular approach to the brachial plexus. Yet in 1961, Brand and Papper (14) reported 84% (194 of a total of 230 procedures) successful supraclavicular brachial blocks while eliciting paresthesias. We did not observe complete failure of sensory blockade when twitches were elicited in muscles of the upper extremity and we related the low frequency of complications to the more accurate location of nerves. Although symptomatic pneumothoraces occurred in 6.1%

of patients reported by Brand and Papper (14), we had no such complications, though asymptomatic small pneumothoraces might have been missed because clinical evaluations and not X-rays were relied on. However, Horner's syndrome occurred in more than 50% of children, especially in patients in whom the tip of the needle was inserted to a depth exceeding 20 mm. This frequency may probably be reduced by improving the technique for inserting the block needle. Insulated needles are not easily advanced into subcutaneous and muscular tissues, and excessive penetration may occur if the skin of the neck is not pinched with a compress: the tip of the needle may still be within the perineural space but close to its medial side rather than, as desirable, close to the lateral side.

The parascalene approach was designed after anatomic studies and theoretical considerations. A similar A-P insertion route has been evaluated at a site of puncture almost identical to that used for Kulenkampff's approach (15). This procedure proved to be reliable in adult patients. No pneumothorax was reported, but the authors stressed that "the needle must not be inserted medial to the lateral border of the anterior scalene muscle if pneumothorax is to be avoided" (15). Anatomic studies on cadavers of children revealed that the cupola of the lung could be injured in more than 50% of cases if such an insertion route was used at such a site of puncture. This study, however, introduced a new concept of penetration into the perineural space that we took into consideration in our procedure.

The parascalene approach that we used in the 60 children of group P proved to be more reliable with significantly less adverse effects than the supraclavicular approach. Both techniques produced anesthesia of almost all infraclavicular branches of the brachial plexus, including axillary and musculocutaneous nerves. The extent of sensory blockade was consistently better than that reported in adults after supraclavicular block (6), except for the skin in the axilla, which was almost never anesthetized in either group (this area is not supplied by nerves from the brachial plexus but rather by the intercostobrachial nerve, a branch of the second thoracic spinal nerve). Although the reason for such a high degree of sensory blockade is not established, it may be caused by 1) better location of the perineural space due to the use of a nerve stimulator; and/or 2) loose attachment of the perineural sheath to the neurolemma sheath of nerves as observed at the emergence of spinal nerves (16), thus allowing more extended spread (especially circumferentially) of local anesthetics. Also, both techniques produced pain relief similar in duration when the same anesthetic solution was used.

As anticipated from our anatomic evaluations, the parascalene technique proved to be almost free of complications and had advantages over supraclavicular approach, even when results with the latter technique were improved by use of a nerve stimulator and insulated needles. The low rate of adverse effects may be related to more accurate location of nerves with the use of a nerve stimulator (as in group S) as well as to the safer insertion route used. Low-voltage electrical impulses, though not discerned by awake children, were sufficient to elicit twitches (which disappeared, in both groups, after <1.5 ml of local anesthetics had been administered).

In conclusion, the use of a nerve stimulator and insulated needles considerably improved the reliability of supraclavicular approaches to the brachial plexus, and we related the low frequency of complications that we observed to the more accurate location of nerves. The parascalene approach proved to be even more reliable and effective and almost free of adverse effects. We recommend this approach to the brachial plexus in children when extensive anesthesia of the upper extremity is required or when axillary approaches cannot be used.

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Effects of Fentanyl and Sufentanil on Peripheral Mammalian Nerves

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GISSEN AJ, GUGINO LD, DATTA S, MILLER J, COVINO BG. Effects of fentanyl and sufentanil on peripheral mammalian nerves. *Anesth Analg* 1987;66:1272-6.

The effects of fentanyl and sufentanil on peripheral nerves were evaluated in isolated sheathed and desheathed rabbit vagus nerves. The action potential amplitudes of A and C fibers were recorded before and after a 30-min exposure to 50 and 100 µg/ml of fentanyl and sufentanil. A reversible decrease in the action potential amplitude of A fibers in desheathed nerves was observed after exposure to 100 µg/ml

of each drug. The action potential amplitude of C fibers was also decreased but not to the same degree as was the A fiber action potential. Pretreatment with naloxone failed to block the reduction in action potential amplitude produced by the two opiates. No evidence of irreversible conduction blockade indicative of local neural toxicity was seen in these studies. The results suggest that high concentrations of fentanyl and sufentanil may exert a weak local anesthetic-type action on peripheral nerves.

Key Words: ANALGESICS—fentanyl, sufentanil. NERVES—fentanyl, sufentanil.

Fentanyl and sufentanil are widely used as intravenous analgesics during balanced anesthetic techniques in surgery. In addition, fentanyl is being administered epidurally to provide postoperative analgesia in surgical patients (1) and as a supplement to epidural local anesthetics in obstetrics (2,3). Recently, sufentanil has also been shown to be effective as an epidural analgesic agent (4). The analgesic action of these agents when injected into the epidural space is believed related to the diffusion of these drugs into the subarachnoid space and their interaction with opiate receptors in the spinal cord. However, little information is available concerning the possible local anesthetic effect of these analgesics. Moreover, there are few data concerning the possible neurotoxicity of epidurally administered fentanyl and sufentanil. Thus, studies were initiated to determine the possible local anesthetic activity of fentanyl and sufentanil in an isolated mammalian nerve preparation and to determine whether there is evidence of localized neural damage.

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Methods

Albino rabbits weighing 2.0–2.5 kg were killed by means of the intravenous administration of a large volume of air. The cervical vagus nerves were rapidly dissected, cleansed of adventitial material, and placed in a HEPES–Liley solution at a pH of 7.3, at a room temperature of 20–22°C and aerated constantly by a stream of 100% O₂. Both sheathed and desheathed nerves were employed in various portions of the study. The details for desheathing of nerves, perfusion of the nerve in a specially prepared nerve chamber, and the method of stimulation and recording of nerve action potentials have been described in a previous publication (5). Recordings of fast-conducting A fibers and slow-conducting C fibers were accomplished in the manner previously described (5). Sheathed nerve fibers were excised vagus nerves cleansed of all adventitial material under a dissecting microscope. Nerve membranes were retained intact. Desheathed nerve fibers were dissected as above but, in addition, the perineurium and epineurium of the nerve was isolated and removed for a 1-cm length. This exposed area was placed in the drug compartment of the isolated nerve chamber.

Solutions of fentanyl and sufentanil were prepared from pure powder (Janssen Pharmaceutica, Inc.) using a HEPES–Liley solution buffered to a pH of 7.3. In some of the experiments, commercial solutions of

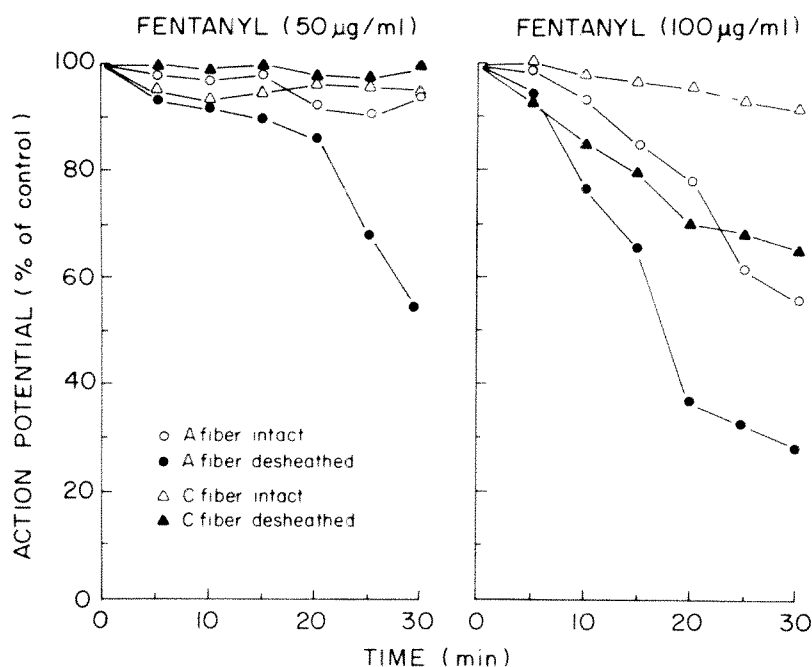


Figure 1. Effect of 50 and 100 $\mu\text{g/ml}$ of fentanyl on action potential amplitude of A and C fibers in sheathed (intact) ($n = 3$) and desheathed ($n = 7$) rabbit vagus nerves.

fentanyl (Sublimaze) were employed. Isolated sheathed and desheathed nerves were allowed to equilibrate in HEPES–Liley solution for approximately 60 minutes while action potential amplitudes were recorded at 5-min intervals. At the end of the 60-min equilibration period, the final value of the compound action potential amplitude was considered the baseline value. However, the baseline values deteriorated with time; after several hours these values could vary $\pm 10\%$. Recovery after drug exposure was even more variable, but all experiments returned to 50% of base value or better after 30–60 minutes of wash time. Three to seven nerves were then exposed to 50 $\mu\text{g/ml}$ and 100 $\mu\text{g/ml}$ of fentanyl or sufentanil. Action potential amplitudes were recorded at 5-min intervals after exposure to fentanyl or sufentanil. After a 30-min exposure, the nerves were washed with a drug-free solution for 60 min while action potential amplitudes were recorded.

In a second series of experiments, six desheathed nerves were pretreated with HEPES–Liley solution containing 4 $\mu\text{g/ml}$ of naloxone for a period of 30 min. The nerves were then perfused with a solution containing either 100 $\mu\text{g/ml}$ of fentanyl ($n = 3$) or 100 $\mu\text{g/ml}$ of sufentanil ($n = 3$) plus 4 $\mu\text{g/ml}$ of naloxone. Perfusion with this solution continued for 30 min, after which the nerves were washed with a drug-free solution. Action potentials were recorded at 10-min intervals during the naloxone exposure period and at 5-min intervals after the addition of fentanyl or sufentanil. Action potentials were also recorded during the washout period.

In the final series of experiments, three sheathed isolated nerve fibers were exposed to commercial solutions of fentanyl containing 50 $\mu\text{g/ml}$ of this agent. In addition, three nerves were exposed to distilled water alone for a period of 30 min. Three nerves were also exposed to commercial fentanyl solutions to which physiological salts were added in the same proportions that were used in the HEPES–Liley solution. Experiments were also carried out in three nerves exposed to commercial fentanyl solution to which physiological salts were added and the pH of the solution adjusted to 6.0, 7.0, or 8.0.

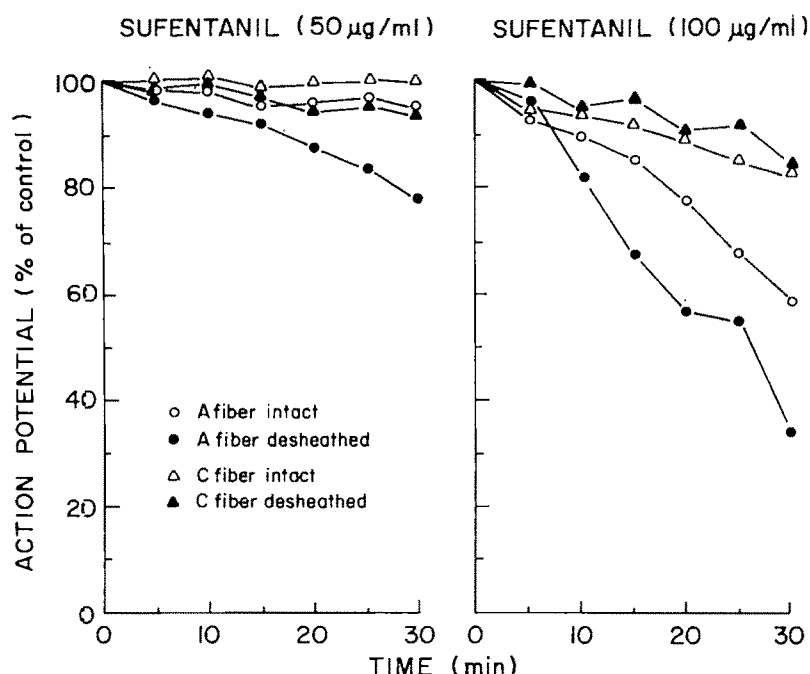
Statistical analysis was performed comparing action potential amplitudes after 30 min of drug exposure with pretreatment baseline values using a paired Student's *t*-test. Comparison between A and C fibers and various drug treatments was accomplished with a nonpaired Student's *t*-test. A *P* value < 0.05 was considered statistically significant.

Results

Fentanyl Studies

Exposure of sheathed nerve fibers to 50 $\mu\text{g/ml}$ of fentanyl did not result in any significant decrease in the height of A or C fiber action potentials throughout the 30-min exposure period (Fig. 1). In the desheathed nerve preparations, the amplitude of the A fiber action potential decreased significantly to 56% of the baseline potential amplitude after 30 min of exposure to 50 $\mu\text{g/ml}$ of fentanyl. No significant change in the

Figure 2. Effect of 50 and 100 $\mu\text{g/ml}$ of sufentanil on action potential amplitude of A and C fibers in sheathed (intact) ($n = 5$) and desheathed ($n = 3$) rabbit vagus nerves.



action potential amplitude of C fibers was observed in the desheathed nerve preparation after 30-min exposure to 50 $\mu\text{g/ml}$ of fentanyl. After exposure of sheathed nerves to 100 $\mu\text{g/ml}$ of fentanyl, the action potential amplitude of the A fibers decreased significantly to 56% of the baseline value after 30 min (Fig. 1). In the desheathed nerve preparation, the A fiber action potential amplitude decreased to 29% of the baseline amplitude after 30-min exposure ($P < 0.05$). The C fiber action potential did not show any significant decrease in amplitude in the sheathed nerve preparation. However, the desheathed nerve preparation showed a decrease in action potential amplitude of C fibers to 65% of the baseline values ($P < 0.05$). During washout of the drug containing solutions, the action potential amplitude of both the sheathed and desheathed nerve fibers returned toward baseline values.

Sufentanil Studies

At a concentration of 50 $\mu\text{g/ml}$ of sufentanil, no significant change in the action potential amplitude of A and C fibers was observed in the sheathed nerves (Fig. 2). In the desheathed nerves, the A fiber action potential decreased to 78% of the control value ($P < 0.05$), whereas no significant change was observed in the action potential amplitude of C fibers. The action potential amplitudes returned toward baseline levels in both A and C fibers after a 60-min washout.

After exposure to 100 $\mu\text{g/ml}$ of sufentanil, a significant decrease in A fiber action potential was ob-

served in both the sheathed and desheathed nerves (Fig. 2). However, the decrease in the action potential amplitude was significantly greater in desheathed than in the sheathed nerves. The C fiber action potentials also decreased to approximately 80% of baseline value in both sheathed and desheathed nerves.

However, the decrease in C fiber action potential amplitude was significantly less than that observed in A fibers. After drug washout, the action potential of all fibers returned toward baseline levels.

Naloxone Interaction with Fentanyl and Sufentanil

As shown in Figures 3 and 4, exposure of desheathed nerve fibers to 4 $\mu\text{g/ml}$ of naloxone had no effect on the action potential amplitude of A and C fibers. However, when 100 $\mu\text{g/ml}$ of fentanyl or sufentanil was added to these solutions containing naloxone, a significant decrease in action potential amplitude of both A and C fibers were observed. The A fiber action potential decreased to 11% of control value when fentanyl was added ($P < 0.05$) and 35% of the control value when sufentanil was administered ($P < 0.05$). The C fiber action potential decreased to 72 and 78% of baseline values when fentanyl and sufentanil were added.

Exposure to Commercial Fentanyl

Exposure of the sheathed isolated nerve to the commercial solution of fentanyl (Sublimaze), which contains 50 $\mu\text{g/ml}$ of fentanyl, resulted in complete in-

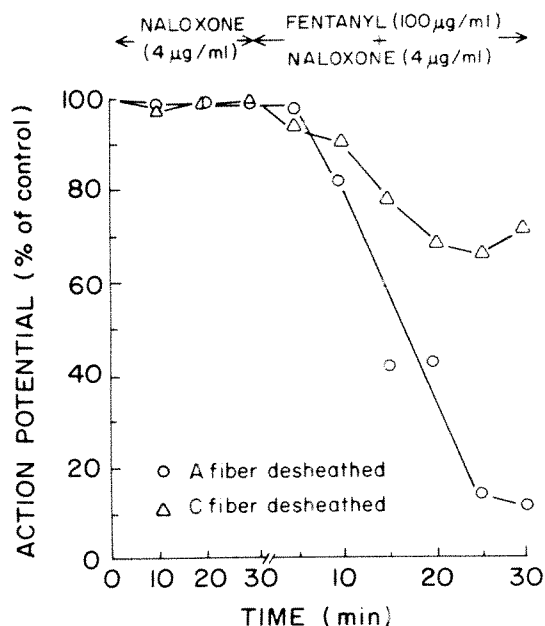


Figure 3. Effect of naloxone ($4 \mu\text{g/ml}$) and fentanyl ($100 \mu\text{g/ml}$) on action potential amplitude of A and C fibers in desheathed rabbit vagus nerves ($n = 3$).

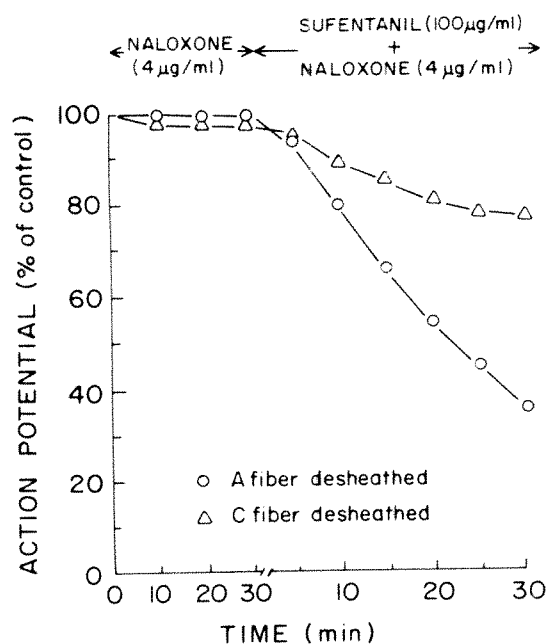


Figure 4. Effect of naloxone ($4 \mu\text{g/ml}$) and sufentanil ($100 \mu\text{g/ml}$) on action potential amplitude of A and C fibers in desheathed rabbit vagus nerves ($n = 3$).

inhibition of A fiber action potentials within 20 min (Fig. 5). After washout of the commercial fentanyl solution, recovery of the action potential amplitude was slow and required approximately 8–10 hr for restoration of the A fiber action potential. Exposure of isolated sheathed nerves to distilled water produced

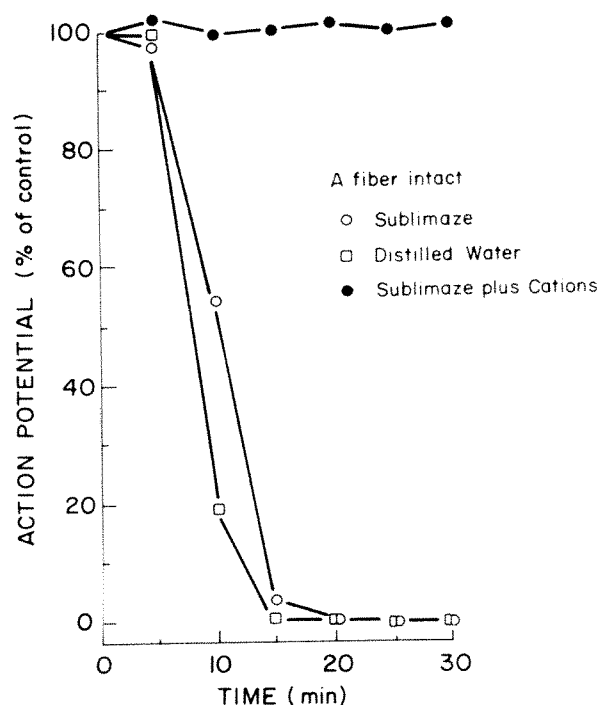


Figure 5. Effect of commercial fentanyl solution (Sublimaze), distilled water, and Sublimaze plus physiological salts on action potential amplitude of A fibers in sheathed (intact) rabbit vagus nerves ($n = 3$).

a similar decrease in action potential amplitude and similarly slow recovery after washout of the distilled water. When physiological salts in proportion to that used in the HEPES–Liley solution were added to commercial solutions of fentanyl, no decrease in A fiber action potential was noted. Finally, when commercial solutions of fentanyl to which physiological salts were added were adjusted to pHs of 6, 7, and 8, and then added to the isolated sheathed nerve, again, no decrease in A fiber action potential was observed.

Discussion

The results of the present study indicate that both fentanyl and sufentanil have minimal effects on conduction in isolated sheathed rabbit vagus nerves. However, in desheathed nerve preparations, both agents significantly decreased the action potential amplitude, particularly of A fibers. The greater depressant effect on A fiber action potentials as compared with C fibers is consistent with previous reports indicating that A fibers are more sensitive than are C fibers in terms of conduction blockade when exposed to local anesthetic (5). The results suggest that at high concentrations both fentanyl and sufentanil may partially suppress conduction in peripheral nerves. The results also indicate that both narcotics apparently do

not diffuse well through a nerve sheath. Thus, it is unlikely that these drugs would cause conduction blockade *in vivo* in peripheral nerves that are enclosed within a nerve sheath. However, in the subarachnoid space, the spinal cord and the spinal nerves are essentially desheathed preparations. Thus, it is possible that the injection of high concentrations of both agents intrathecally might cause some degree of conduction blockade similar to that produced by local anesthetics. The depressant effect on A and C fibers action potential in desheathed peripheral nerves is probably not related to the presence of opiate receptors in these nerves, because pretreatment with naloxone failed to inhibit the decrease in action potential produced by fentanyl and sufentanil. Furthermore, although sufentanil is considerably more potent as an analgesic agent than fentanyl when administered intravenously or epidurally (4,6) in the present study, there was no difference in potency between the two agents with regard to their ability to decrease A and C fiber action potentials. This also suggests that the effect of these narcotics on peripheral nerves is not related to an effect on opiate receptors. This agrees with the observation that there is a virtual absence of opiate receptors in spinal ventral roots and in peripheral nerves (7).

The decrease in action potential amplitude in the desheathed nerve preparation suggests that although the analgesic action of fentanyl and sufentanil after epidural or intrathecal administration is related primarily to their interaction with opiate receptors in the spinal column, they also may cause some depression of nerve transmission similar to that produced by local anesthetic agents. In this regard, evidence has been presented by various investigators that opiates may have a dual mechanism of action (8,9). The primary clinical effect is related to interaction with opiate receptors in the spinal cord. However, at high concentrations they may also possess an effect similar to that seen with local anesthetics. Whether this latter effect is of importance clinically is difficult to determine. The large concentrations of fentanyl and sufentanil required to show significant depression of A and C fiber action potentials suggest that the local anesthetic-like action of these agents is probably of little significance clinically.

The other aspect of this study concerns the possible neurotoxicity of fentanyl and sufentanil. Although these agents have been administered into the epidural and subarachnoid space of humans, there is little information concerning the potential neurotoxic effect of these opiates. Kosterlitz and Wallis reported previously that morphine failed to produce any deleterious effect on myelinated or nonmyelinated fibers in mammalian nerves (10). The current study also indicates that fentanyl and sufentanil solutions containing physiological salts do not exert any prolonged effect on peripheral nerve conduction. However, exposure of nerves to commercial solutions of fentanyl resulted in profound conduction blockade and delayed recovery similar to effects seen with distilled water. This suggests that fentanyl or sufentanil should be diluted in saline before administration into the epidural or subarachnoid space.

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Opioid Analgesia at Peripheral Sites: A Target for Opioids Released during Stress and Inflammation?

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JORIS JL, DUBNER R, HARGREAVES KM. Opioid analgesia at peripheral sites: a target for opioids released during stress and inflammation? *Anesth Analg* 1987;66:1277-81.

The peripheral analgesic effects of opiates were evaluated in a rat model of inflammation. The experimental design excluded a potential central nervous system site of action for the observed analgesia. After the injection of carrageenan (CARRA) in the plantar surface of both hind paws, an opiate was injected into one paw and saline was injected into the other paw. The inflamed paws injected with the μ -agonist, fentanyl (0.3 μ g) or the κ -agonist, ethylketocyclazocine (10 μ g) were significantly less hyperalgesic ($P < 0.001$ and

$P < 0.01$, respectively) than were the contralateral inflamed paws injected with saline. At these doses, fentanyl and ethylketocyclazocine were devoid of systemic effects. Another μ -agonist, levorphanol (20, 40, 80, or 160 μ g) and dextrorphan (160 μ g), its dextrorotatory isomer, were used next to evaluate opioid specificity. Levorphanol produced a dose-related blockade of CARRA-induced hyperalgesia ($P < 0.005$). In contrast, 160 μ g of dextrorphan was inactive. These results demonstrate that local administration of opiates into an inflamed paw produces a dose-related, stereospecific analgesia restricted to the injected area.

Key Words: ANALGESICS—fentanyl, ethylketocyclazocine, levorphanol, dextrorphan.

It is widely recognized that opiates and opioid peptides produce analgesia through activation of opioid receptors located at spinal and supraspinal levels (1-3). Although opioid receptors have been demonstrated on primary afferent nerve fibers (4,5), it is not known if these peripheral receptors contribute to the analgesic activity of opiates and opioid peptides.

Recently, peripheral analgesic effects of opiates have been evaluated after injection into either the perineural space (6-8) or directly into the subcutaneous tissue (9,10). After perineural administration of opiates in patients, significant pain relief has been reported in some (6,8) but not all studies (7). Peripheral effects of opiate agonists have been suggested after subcutaneous injection into rat paws sensitized with prostaglandin E_2 (9). In an actual model of inflammation, peripheral agonist-like activity using opiate antagonists has been reported (10). However, the pharmacologic specificity of opiate agonists administered at peripheral sites of inflammation is unknown.

Carrageenan (CARRA) has been employed widely as an animal model of inflammation to screen for clin-

ically useful nonsteroidal anti-inflammatory drugs (11). The present study used this model of inflammation to demonstrate opioid receptor specificity, stereoselectivity, and the dose-dependent relation of peripheral opiate agonists in the modulation of thermal hyperalgesia secondary to this inflammation.

Methods

This study was approved by the animal investigation committee of the National Institute of Dental Research. Male Sprague Dawley rats (Charles River, Inc.; weight, 250-300 g) were maintained in an animal room (lights on 6 AM to 6 PM) with water and food ad libitum for at least 1 week before testing. All studies employed randomized vehicle-controlled designs with observers unaware of treatment allocation.

Hyperalgesia was determined using thermal stimulation. Unrestrained rats were placed within a transparent plastic chamber with a glass floor. After a 5-minute habituation period, the plantar surface of their paws was exposed to a beam of radiant heat. Paw withdrawal latency (PWL) was taken as an index of nociceptive threshold. Previous studies have demonstrated that organized intentional behaviors from which pain and analgesia can be inferred are correlated with withdrawal latency in this method (12).

In a first study, the peripheral effect of the μ -agonist fentanyl (FEN) (Janssen Pharmaceutica) was

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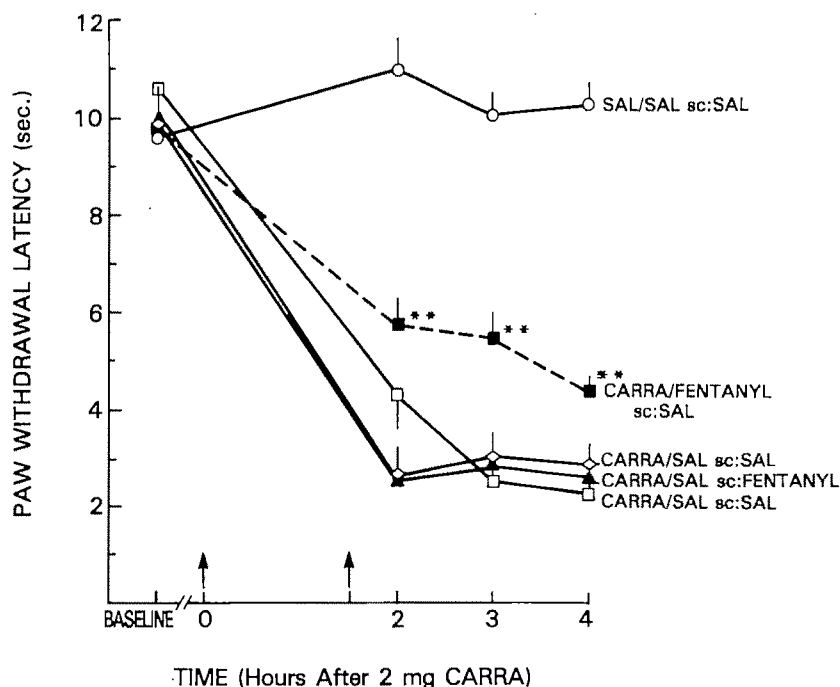


Figure 1. Peripheral analgesic effect of fentanyl (FEN) (0.3 μ g). One group received initial injections of saline (SAL) into the plantar surface of both hind paws at time 0 (first arrow), and 90 minutes later (second arrow) received injections of SAL into both hind paws and subcutaneously (sc.) into the neck (SAL/SAL sc:SAL, open circles). The three other groups received initial injections of carrageenan (CARRA). Ninety minutes later, one CARRA group received a subcutaneous injection of SAL into the neck and FEN (0.3 μ g) into one inflamed paw (CARRA/FENTANYL sc:SAL, filled squares) and SAL in the other inflamed paw (CARRA/SAL sc:SAL, open squares). At the same time, another CARRA group received SAL injections into both paws and the same dose of FEN injected into the neck (CARRA/SAL sc:FENTANYL, filled triangles). The last CARRA group (CARRA/SAL sc:SAL, open diamonds) received SAL into the paws and the neck. The circles, the triangles and the diamonds represent the mean latencies of hind paws, both of which had received the same treatment. ** $P < 0.01$ as compared with the contralateral paw of the rats receiving the opiate into one of the inflamed paws.

assessed. One group ($n = 7$) received initial injections (0.1 ml) of saline (SAL) into the plantar surface of both hind paws at time 0, and 90 minutes later received injections of SAL into both paws and subcutaneously (SC) into the neck. Three other groups ($n = 7-10$) received initial injections (0.1 ml) of 2 mg of λ -CARRA (Sigma Chemical Co., C-3889) into both paws. Ninety minutes later, one CARRA group received an injection of 0.3 μ g FEN into one inflamed paw, while SAL was injected into the other inflamed paw and injected SC into the neck. At the same time, another CARRA group received SAL injections into both paws and the same dose of FEN (0.3 μ g) injected into the neck. The last CARRA group received SAL injections in both paws and in the neck. Rats were tested once at baseline and 2, 3, and 4 hours after the initial paw injections.

The same experimental design was used to evaluate the peripheral analgesic effect of 10 μ g of ethylketocyclazocine (EKC) (Sterling Winthrop Res. Inst.), a κ -opiate agonist, instead of FEN.

In the last experiment, the dose-response relation and the stereoselectivity of the peripheral opiate effect were determined using another μ -agonist, levorphanol (Hoffmann-La Roche Inc.), and its inactive dextrorotatory isomer, dextrorphan (Hoffmann-La Roche Inc.). Carrageenan ($n = 6$) was injected into both paws and 90 minutes later SAL was injected into one hind paw, while the other inflamed paw was

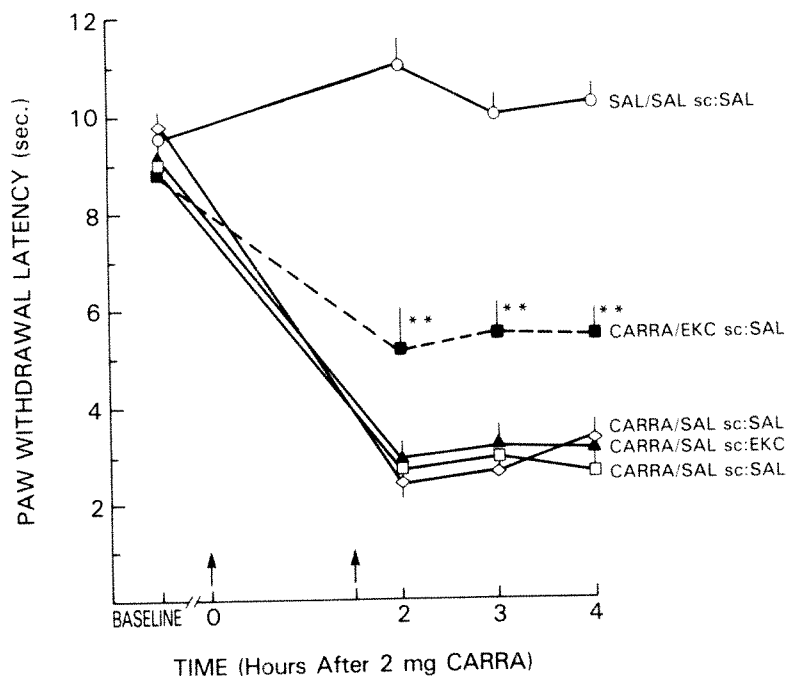
injected with either levorphanol (20, 40, 80, or 160 μ g) or dextrorphan (160 μ g). Rats were tested once at baseline and 2, 3, and 4 hours after the CARRA injections.

Statistical analysis was carried out using analysis of variance (ANOVA) for repeated measures for overall effect, with Duncan's multiple range test for comparison between groups (13). To determine a dose-response relation for levorphanol, a linear regression ANOVA tested the zero slope hypothesis (13). Values are quoted in the text as means $\pm$ SEM. In the first two studies, three of the four groups had the same drugs administered into both hind paws. For each of these groups, the mean latencies of both paws were used to determine the group mean. In the remaining group, which received a hind paw injection of opiate, each paw was analyzed separately, because one paw received the CARRA-opiate combination, whereas the other paw was injected with CARRA and SAL.

Results

In the FEN experiment, the injection of CARRA into both paws followed by SAL resulted in a profound decrease in PWL ($P < 0.01$) as compared to the control group receiving SAL for all injections (Fig. 1). In rats injected with CARRA followed by opiate into one paw, the inflamed paws injected with 0.3 μ g FEN

Figure 2. Peripheral analgesic effect of ethylketocyclazocine (EKC) (10 μ g) using the same experimental design as in Figure 1. $**P < 0.01$ as compared with the contralateral paw of the rats receiving the opiate into one of the inflamed paws.



were significantly less hyperalgesic ($F[1,9] = 27.25$; $P < 0.001$) than were the contralateral inflamed paws injected with SAL. This peripheral analgesic effect persisted for more than 2 hours (Fig. 1). In contrast, the same dose of FEN had no effect when administered SC into a distant site in the neck.

Figure 2 shows similar results after peripheral administration of the κ -agonist, EKC. Administration of CARRA into both paws followed by SAL injections resulted in sustained hyperalgesia ($P < 0.01$) as compared to rats administered SAL only. In the group receiving CARRA followed by a peripheral opiate injection into one paw, 10 μ g EKC produced a significant peripheral analgesia ($F[1,9] = 13.6$; $P < 0.01$) compared with contralateral inflamed paws injected with SAL (Fig. 2). This effect persisted for more than 2 hours. In contrast, EKC had no effect when systemically administered.

Administration of levorphanol into an inflamed paw produced a peripheral dose-related analgesia ($F[1,20] = 11.9$; $P < 0.005$) as compared with the inflamed contralateral paw injected with SAL (Fig. 3). The analgesic effect was most clearly evident with the 40 μ g ($P < 0.05$), 80 μ g ($P < 0.01$), and 160 μ g ($P < 0.01$) doses. This peripheral analgesic effect was stereoselective, because administration of 160 μ g of dextrorphan did not alter the nociceptive threshold (Fig. 3). Levorphanol at these doses had no systemic effect because the contralateral saline-injected paws exhib-

ited neither a significant difference between any groups nor a dose-response relation.

Discussion

These results demonstrate that local administration of an opiate into an inflamed paw produces a dose-related analgesia restricted to the inflamed paw. These effects are opioid receptor-specific because levorphanol is analgesic, whereas its dextrorotatory isomer, dextrorphan, is inactive when administered into the inflamed paw. An additional test to determine opioid specificity, naloxone challenge, was avoided because of its reported agonist-like effects in this model of inflammation (10).

If opiates were to act only in the central nervous system to produce analgesia, then a bilateral analgesic effect should have been observed in both inflamed hind paws, regardless of the site of administration. However, systemic administration of these low doses of FEN and EKC subcutaneously into the neck had no effect, whereas peripheral administration into an inflamed paw produced localized analgesia. Additional evidence for lack of a systemic opiate effect is the similar latencies for the SAL-injected contralateral paws of the group receiving local opiate and for the CARRA group receiving no opiate. Finally, the latencies of the SAL-treated paws of the four levorphanol groups were statistically indistinguishable, despite

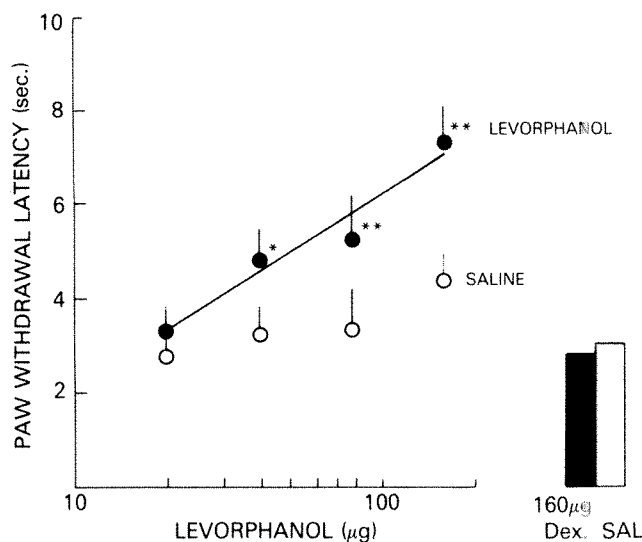


Figure 3. Dose-response relation and stereoselectivity for the peripheral analgesic effects of levorphanol ($n = 6/\text{group}$). Carrageenan was injected into both hind paws and 90 minutes later saline was injected into one hind paw while the other hind paw was injected with either levorphanol (20, 40, 80, or 160 μg) or dextrorphan (160 μg). Rats were tested 3 hours after the CARRA injection. The asterisks denote significant differences in the paw withdrawal latencies of the levorphanol-treated paws (filled circles) and the contralateral saline-treated paws (corresponding open circles) with $*P < 0.05$ and $**P < 0.01$. There was no significant difference for the paw withdrawal latency of dextrorphan (filled histogram) and the contralateral saline-treated paws (open histogram).

the dose-related analgesia observed in the opiate-treated paws. We interpret these results to indicate that opiate-induced analgesia is due to a peripheral mechanism as well as to its well recognized central mechanism of action. The peripheral analgesic effect is observed with both μ - and κ -agonists.

These results raise the question of the mechanism of this peripheral opiate effect. The two most likely targets are peripheral terminals of primary afferents and leukocytes, both of which are known to possess opioid receptors (4,5,14,15). An opioid effect on the nerve terminals may be direct, by modulating nociceptive transmission (16,17), or it may be indirect, by an anti-inflammatory effect (14,15,18,19).

Although opioid receptor binding sites have been detected in peripheral nerve trunks (4,5), the effects of opiates administered perineurally have been equivocal. Morphine alters the compound action potential in some studies (16,17), whereas others have either not observed this effect (20) or ascribed it to the presence of drug preservatives (21). In addition, perineural administration of opiates reduces patient report of pain in some (6,8) but not all studies (7). Our finding that preservative-free opiates consistently produce analgesia when administered into inflamed

peripheral tissue suggests that this may be a more accurate method for evaluating peripheral analgesic actions of opiates than is perineural administration. This proposition is supported by the fact that opioid receptors may be more highly concentrated in the nerve terminal, due to a preponderance of peripherally directed axonal transport (4,22) and to the fact that these peripheral opioid receptors are functionally active under conditions of inflammation. In addition, opiate receptors located on non-neural elements (e.g., leukocytes) may participate in the modulation of peripheral inflammation and accompanying pain.

In addition, the present findings have potential therapeutic implications. Several undesirable side effects of opiates result from their actions in the CNS. When injected peripherally in inflamed tissue, small doses devoid of central effects may provide prolonged analgesia restricted to this area. Furthermore, the development of quaternary opiates that would not cross the blood-brain barrier and therefore activate only peripheral opioid receptors might lead to analgesic drugs lacking centrally mediated side effects of the opiates (23,24). Such drugs would be of potential clinical utility in the management of analgesia and anesthesia.

The participation of a peripheral mechanism in opiate analgesia may provide a potential target for circulating opioid peptides such as pituitary beta-endorphin. For example, elevation of plasma beta-endorphin by administration of corticotropin releasing factor decreases postoperative pain (25), whereas suppression of beta-endorphin levels by administration of low levels of dexamethasone increases postoperative pain (26). Results from the present study suggest that one potential target for these circulating opioids is the peripheral modulation of nociception.

In conclusion, we have demonstrated that peripheral administration of opiates in the site of acute inflammation produces analgesia. This effect is peripherally mediated, opioid-specific and dose-related. Peripheral terminals of primary afferents and leukocytes represent the most likely targets for this effect. These findings may have therapeutic implications through the use of a new route for the delivery of opiates or by the development of quaternary opiates with the potential to avoid centrally mediated side effects.

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The Effect of Meperidine on the Guinea Pig Extrahepatic Biliary Tract

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GOLDBERG M, VATASHSKY E, HASKEL Y, SEROR D, NISSAN S, HANANI M. The effect of meperidine on the guinea pig extrahepatic biliary tract. *Anesth Analg* 1987;66:1282-6.

The effect of meperidine on the mechanical activity of isolated guinea pig common bile duct (CBD) and gallbladder was studied in vitro. The effect was found to consist of inhibitory and excitatory phases. The inhibitory phase, characterized by a decrease in the response of the CBD and gallbladder to carbachol and electrical stimulation, was seen with con-

centrations of 10^{-6} M or higher. The excitatory phase, seen at high concentrations of meperidine (5×10^{-5} – 10^{-4} M), involved an increase in spontaneous contractions of CBD and in the tone of the gallbladder. Neither effect of meperidine was affected by 0.5×10^{-5} M naloxone. These data indicate that meperidine acts on the biliary tract by a mechanism different from that associated with the effect of morphine.

Key Words: LIVER—bile ducts. ANALGESICS—meperidine.

Meperidine, a synthetic opiate analgesic, is widely used in the management of surgical patients, including the nonoperative management of hepatobiliary and pancreatic disorders and biliary colic. Like other opiates, meperidine has been found to increase intrabiliary pressure, although in this respect it is less potent than morphine or fentanyl (1). The increase of the intrabiliary pressure produced by narcotics may adversely affect hepatobiliary disease and confuse the interpretation of operative cholangiography (2,3). Greater understanding of the mechanism of meperidine action would be of value.

To date, most of the studies on the extrahepatic biliary tract have been performed in humans and animals by cannulation of the common bile duct (CBD). In these experiments, narcotic drugs were administered systemically and the exact site of their action was not well defined. Recently, isolated preparations of guinea pig CBD and gallbladder were used for investigating the effects of morphine and endogenous opioid peptides (4–6). It was found that morphine

reduced the release of acetylcholine (ACh) from cholinergic nerves in the terminal CBD but not in the gallbladder (5). On the basis of this finding and the blockade of the morphine effect on the CBD by naloxone, it was suggested that opiate receptors are present in the CBD. This raises the possibility that meperidine may also have local effects on the biliary tract. In the present study an in vitro model was used to examine the effects of meperidine on the guinea pig CBD and gallbladder.

Materials and Methods

A total of 41 guinea pigs of both sexes, weighing 350–600 g, were used. The animals were stunned and bled to death, and the gallbladder and CBD (not including the ampulla) were carefully dissected and removed. Each preparation was separated into gallbladder and CBD (from the junction of the cystic duct and common hepatic duct to the ampulla). The gallbladder was opened longitudinally and a strip 12 mm long and 2 mm wide was excised.

The preparations were mounted in an organ bath (10 ml) filled with Krebs solution through which 95% O_2 in 5% CO_2 was bubbled. The bath temperature was maintained at 37°C. One end of the preparation was fixed to a tissue holder; the other end was fixed to an isometric force transducer (Statham, model UC2). The resting force was 200 mg for the CBD and 300 mg for

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the gallbladder. For electrical field stimulation the preparations were set vertically between two platinum ring electrodes connected to a Grass model S-88 electrical stimulator. Contractile responses were recorded on a Gould model 2200-S chart recorder.

The electrical stimulation was 40 V, 0.5 msec duration at 0.2–15 Hz, for 10 sec. The CBD was left for 1 hr until full equilibration (10 min of steady recording of spontaneous activity). An equilibration period of 3 hr was found to be necessary for the gallbladder. The preparations were kept in the bath for 2–3 hr after the equilibration period. Between applications of drugs, the solution within the organ bath was replaced several times until recovery of the basal activity and response to electrical stimulation were restored to control levels.

In case of incomplete recovery, the responses to electrical stimulation at various frequencies were repeated and this measurement was used as a new control. Between each electrical stimulus an interval of at least 2 min was maintained. The solution of drugs was in the bath for 5 min before experiments were initiated.

Tetrodotoxin (TTX), a nerve blocking agent, was used to examine whether meperidine acts via neural pathway or directly on the smooth muscle. Carbachol, a cholinergic muscarinic agonist, was used to study the possible antimuscarinic effect of meperidine. Atropine was used to test whether meperidine action was mediated by muscarinic receptors.

The lowest concentration at which the effect of meperidine became significant was determined by a paired difference *t*-test. The statistical significance between the effects at different concentrations was examined by the analysis of variance procedure (ANOVA). For both tests the effect was considered significant when $P < 0.02$.

The following drugs were used: 10^{-6} – 10^{-4} M meperidine-HCl (Teva Pharmaceutical Ind., Israel); 10^{-7} – 10^{-5} M naloxone (Du Pont); and 10^{-6} M tetrodotoxin, 10^{-7} – 10^{-6} M carbamylcholine chloride (carbachol), and 10^{-6} M atropine sulfate (all from Sigma).

Results

The Effect of Meperidine on the Response of the CBD and Gallbladder to Electrical Stimulation

Guinea pig CBD and gallbladder contracted in response to electrical field stimulation. In the CBD, this contraction was usually followed by relaxation. The amplitude of the contractile response increased as the frequency of the electrical stimulus increased. Tetrodotoxin (10^{-6} M) and 10^{-6} M atropine blocked the contraction produced by the electrical stimulation.

Meperidine decreased the contraction of the CBD

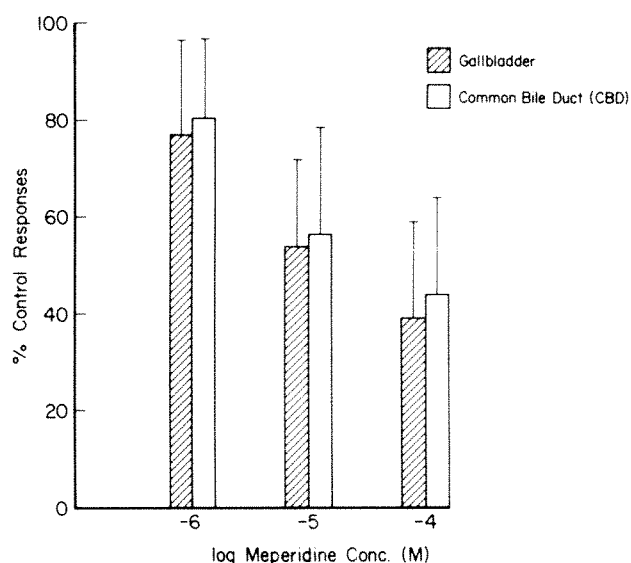


Figure 1. Concentration-dependent inhibitory effect of meperidine on the CBD and gallbladder response to electrical stimulation. The statistical significance of the difference between the average of contraction response versus meperidine concentration was tested by the analysis of variance procedure (ANOVA), under the null hypothesis of no significant difference. The difference were found to be statistically significant for both CBD ($F = 22.584$, $d.f. = 4, 147$, $P < 0.02$) and gallbladder ($F = 24.319$, $d.f. = 2, 68$, $P < 0.02$).

and gallbladder elicited by electrical stimulation. The lowest concentration that produced this effect was 10^{-6} M, as determined by the paired difference *t*-test ($P < 0.02$). Meperidine acted in a concentration-dependent manner ($n = 17$ for CBD, $n = 15$ for gallbladder) (Fig. 1). The statistical significance of this dependence was by the ANOVA procedure ($P < 0.02$). This suppression effect of meperidine was not affected by naloxone 0.5×10^{-5} M ($n = 10$). Meperidine at a concentration of 5×10^{-5} M or more changed the pattern of the CBD response to electrical stimulation to relaxation followed by contraction.

The Effect of Meperidine on the CBD and Gallbladder Response to Carbachol

Carbachol in the range of 10^{-7} to 10^{-6} M induced concentration-dependent contraction of the CBD and gallbladder. Meperidine (10^{-6} M or higher) decreased the effect of carbachol on the CBD and gallbladder in a concentration-dependent manner ($n = 5$) (Fig. 2). This inhibitory effect was not blocked by naloxone 0.5×10^{-5} M ($n = 2$).

The Effect of Meperidine on Spontaneous Contractions of the CBD

In the guinea pig CBD, meperidine had no effect on spontaneous contractions in concentrations up to 2

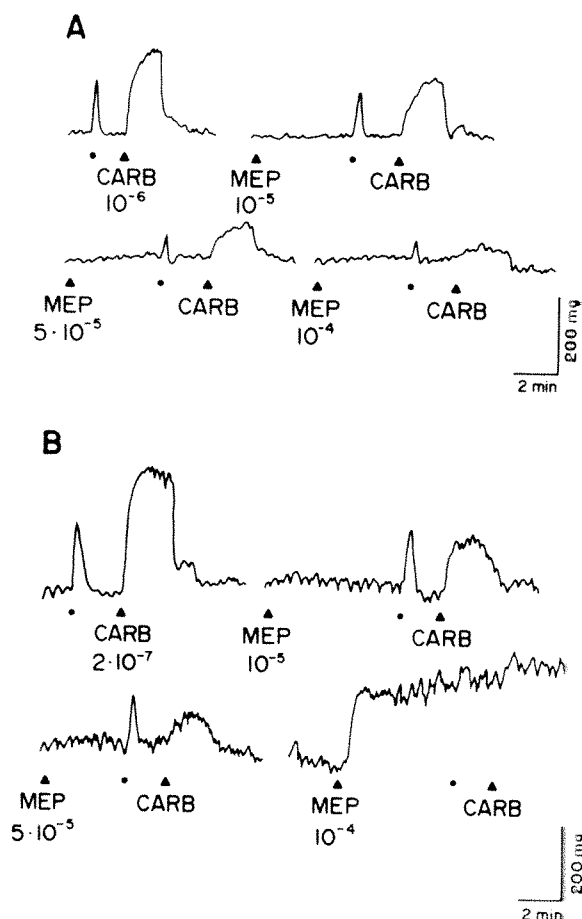


Figure 2. Concentration-dependent antagonism by meperidine of responses of the CBD (A) and gallbladder (B) to carbachol. Abbreviations: MEP, meperidine; CARB, carbachol. Each dot represents 40 V, 2 Hz, 10 sec electrical stimulus. (A) Repeated doses of 10^{-6} M carbachol. (B) Repeated doses of 2×10^{-7} M carbachol. Between each dose of meperidine, the solution was replaced several times with restoration of the baseline responses to carbachol.

$\times 10^{-5}$ M. At concentrations of 5×10^{-5} and 10^{-4} M, meperidine increased the amplitude of the spontaneous contractions ($n = 10$ out of 14) (Fig. 3). This effect was not altered by naloxone 0.5×10^{-5} M ($n = 10$). Tetrodotoxin at a concentration of 10^{-6} M, which blocked the response to electrical stimulation, had no effect on the augmentation of spontaneous contractions induced by meperidine ($n = 4$).

Atropine (10^{-6} M) added to the bath before addition of meperidine did not prevent the increase in spontaneous contractions caused by meperidine ($n = 5$).

The Effect of Meperidine on the Tone of the Gallbladder

Meperidine increased the tone of the gallbladder at concentrations of 5×10^{-5} and 10^{-4} M ($n = 14$) (Fig. 4). The effect of meperidine was not altered by nal-

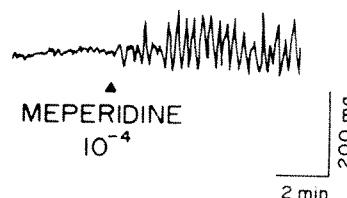


Figure 3. The excitatory effect of 10^{-4} M meperidine on the spontaneous contractions of the CBD.

oxone at concentrations of 10^{-7} and 10^{-6} M ($n = 4$). Higher concentrations of 0.5×10^{-5} and 10^{-5} M naloxone reversed the effect of meperidine on gallbladder tone. However, naloxone also decreased the basal tone of the gallbladder in the absence of meperidine ($n = 8$). Tetrodotoxin (10^{-6} M) did not affect the excitatory effect of meperidine on the gallbladder tone ($n = 4$). The effect of meperidine on the tone of the gallbladder was not altered by atropine-induced muscarinic blockade ($n = 3$), as seen for the CBD.

Discussion

The peripheral actions of opiate analgesics are well recognized (1,7), but little is known concerning the mechanisms involved. In the present work we employed an in vitro method to investigate the mechanisms underlying the effect of meperidine on the guinea pig gallbladder and common bile duct. The results show that meperidine inhibits the contractile responses induced by electrical stimulation. This effect was not antagonized by naloxone. At high concentrations ($>5 \times 10^{-5}$ M) meperidine had an excitatory influence that also appears to be mediated by a non-opiate mechanism.

Previous studies demonstrated that morphine and related substances inhibit the electrically evoked release of acetylcholine from nerves in the intestine (8) and gallbladder (9). The site of this activity is believed to be opiate receptors located on cholinergic nerve terminals (10). Because the inhibitory effect of meperidine in the present study was not blocked by naloxone, it seems that it does not act by such a mechanism. However, we found that meperidine inhibits the contractile response of the gallbladder and CBD to the muscarinic agonist carbachol. Such an atropine-like effect had been mentioned several times in the literature (11), but there are studies showing that meperidine does not block the effects of cholinergic muscarinic agonists (12,13). In these studies the muscarinic effects were measured in intact animals where the drugs may have both central and local effects. In the present work, isolated tissue were employed and therefore only local effects were measured. We there-

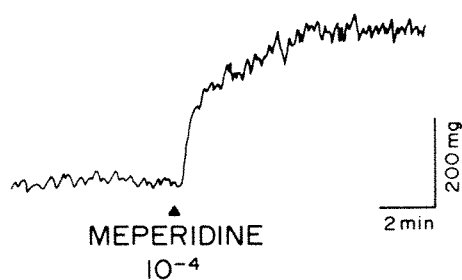


Figure 4. The excitatory effect of 10^{-4} M meperidine on the tone of the gallbladder.

fore conclude that the meperidine inhibitory action on the electrically evoked response is largely because of its antimuscarinic properties. Such activity by meperidine has been noted by Paton (8) in the guinea pig ileum. In contrast to the direct antimuscarinic effect of meperidine on the guinea pig CBD and gallbladder, morphine does not have such a direct anticholinergic action in the same model (5). Thus, although there is no dispute concerning the important nerve-mediated effects of opiate analgesics on the biliary tract (4,5) and other peripheral systems, their direct effects cannot be ignored.

At high concentrations, meperidine enhanced the amplitude of the spontaneous contractions in the CBD and raised the tone in the gallbladder (Fig. 3 and 4). This finding is compatible with the previous observation that meperidine, when given systemically, increased the intrabiliary pressure in the human (1). This present observation was made in the presence of atropine, indicating that muscarinic receptors were not involved in this effect. It may be suggested that meperidine induced the release of an excitatory substance from the nerves. However, this effect was not altered in the presence of the nerve blocker tetrodotoxin. It therefore can be concluded that the site of the excitatory actions is the smooth muscle itself. Similar contractile effects by opiates and enkephalins have been reported on various smooth muscles from the gastrointestinal tract (14,15).

In contrast to this excitatory effect of meperidine, Asoaka and Oochi (5) found that morphine had an inhibitory effect on the spontaneous contraction of the guinea pig CBD and ampulla, which was inhibited by naloxone and TTX. Thus, they suggested the presence of inhibitory neural opiate receptors in the guinea pig CBD and ampulla.

In the present study the excitatory effect of meperidine was not opposed by low concentrations of naloxone, whereas higher concentrations were found to have an inhibitory effect on the basal tone of the gallbladder. Behar et al. (16) also found that naloxone

inhibited the motor activity of the cat sphincter of Oddi. On the basis of these present findings, it seems that the excitatory effect of meperidine on the guinea pig CBD and gallbladder is not mediated by opiate receptors. An obvious question is how these results related to the actions of meperidine in the human subject. First, it is appropriate to compare the concentrations. In surgical patients, the minimum effective analgesic concentrations of meperidine in the plasma are 0.24–0.76 $\mu\text{g/ml}$ (17). (These concentrations are achieved by the administration of 0.7–1.4 mg/kg body weight.) These plasma concentrations correspond to approximately 10^{-6} – 3×10^{-6} M. However, meperidine is used as an adjunct to anesthesia for major surgical procedures in doses of 2–5 mg/kg (18), producing during the first hour after injection plasma concentrations of 2–5 $\mu\text{g/ml}$ (approximately 10^{-5} – 2×10^{-5} M). Thus, the concentrations employed in the present study widely overlap the range encountered under clinical conditions. It must be remembered that the exact local concentrations in human tissues is not known, so any comparison can be only qualitative.

Most of the observations were similar for both the CBD and gallbladder. In both organs, meperidine antagonized the response to electrical stimulation and to carbachol. As to the excitatory action, meperidine raised the tone of the gallbladder, whereas in the CBD it enhanced the spontaneous contractions. The concentration dependence for both organs was similar.

In conclusion, meperidine has a dual effect on the guinea pig extrahepatic biliary tract, different from that of morphine and not mediated via opiate receptors: 1) An inhibitory effect on the biliary tract responses to electrical stimulation that is probably related to its antimuscarinic activity, 2) An excitatory effect on the spontaneous contractions of the CBD and the tone of the gallbladder that is mediated by direct action on the smooth muscle. This effect is not mediated by a cholinergic mechanism.

Further investigations are required for full comprehension of the opiate's effect on the extrahepatic biliary tree. We can only speculate that systemically administered meperidine, because of its local antimuscarinic activity, is less potent than morphine in increasing intrabiliary pressure.

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The Enflurane-Sparing Effect of Alfentanil in Dogs

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HALL RI, SZLAM F, HUG CC Jr. The enflurane-sparing effect of alfentanil in dogs. *Anesth Analg* 1987;66:1287-91.

Some investigators believe that the dog is less sensitive than are humans to the anesthetic/analgesic actions of opioids. The alfentanil plasma concentration [ALF] vs anesthetic effect relationship has been determined for humans undergoing surgery. This study was designed to determine the [ALF] vs anesthetic relationship for alfentanil in the enflurane-anesthetized dog and thereby to provide data by which the [ALF] vs anesthetic effect relationships in the dog and in humans could be compared. Mongrel dogs (n = 10) were anesthetized with enflurane, and enflurane MAC (EMAC) was determined in each dog. After this, each dog received at least three incremental infusions of alfentanil using infusion rates of 0.625, 1.6, 8, 32, or 80 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. EMAC and [ALF] were determined during each infusion rate. There was a linear increase in [ALF] produced by incremental infusions of alfentanil ($r = 0.999$). Administration of alfentanil produced a dose-dependent reduction of EMAC up to a maximum of $72.5 \pm 3.7\%$ (mean $\pm$ SEM) at 32 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ([ALF] = 960 ± 86 ng/ml); a ceiling effect was evident. The degree of EMAC reduction (69%)

produced by an infusion rate of 8 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ([ALF] = 223 ± 13 ng/ml) was not statistically different from the EMAC reductions produced by infusion rates of 32 (73% reduction at [ALF] = 960 ± 86 ng/ml) or 80 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (70% reduction at [ALF] = 2613 ± 247 ng/ml) ($P > 0.05$). The relative potency of alfentanil was one-seventh to one-tenth that of fentanyl studied under identical conditions. The [ALF] producing maximal EMAC reduction in the enflurane anesthetized dog in response to tail-clamp stimulus (223 ng/ml) was similar to the [ALF] required to provide adequate anesthesia of patients for skin incision in the presence of nitrous oxide (mean plasma concentration required to prevent response to skin incision, 279 ± 20 ng/ml; 95% confidence interval, 238-320 ng/ml). It is concluded that alfentanil, in common with other μ -receptor agonists, is capable of reducing enflurane MAC by only 70% in dogs. The anesthetic efficacy of alfentanil in humans and in the dog appears to be similar.

Key Words: ANALGESICS—alfentanil. ANESTHETICS, INTRAVENOUS—alfentanil. ANESTHETICS, VOLATILE—enflurane.

Alfentanil is a short-acting opioid analgesic with a pharmacokinetic profile favorable to its administration by continuous variable-rate infusion (1). The concentration vs anesthetic effect relationships for alfentanil have been determined in patients anesthetized with 66% nitrous oxide for general surgical procedures (2). Studies in animals have demonstrated a limited anesthetic efficacy (at least in terms of ability to reduce the MAC of volatile agents) for all the μ -receptor agonists studied to date (3-8). By obtaining information about the anesthetic efficacy vs plasma alfentanil concentration in the dog, we would be able

to compare alfentanil's efficacy in dogs and humans. Dogs are thought to be less sensitive to opioid anesthesia than are humans and the relevance of the data obtained from the animal model has therefore been debated (9,10). Also, the ability to compare potency ratios of different opioids on the basis of their plasma concentrations for equivalent degrees of effect under identical conditions is important. Such comparisons under stable conditions (i.e., stable drug concentrations and constant experimental variables) avoid the problems of comparing the potency and efficacy of drugs with different pharmacokinetic profiles (e.g., alfentanil vs fentanyl). This study was undertaken 1) to determine the concentration vs anesthetic effect relationship for alfentanil in the enflurane anesthetized dog; 2) to provide data for comparison of the alfentanil concentration vs anesthetic effect relationship in the dog and in humans using stimuli that are said to be equivalent (tail-clamp and skin incision) (11); and 3) to determine the relative potencies of alfentanil and fentanyl in terms of enflurane MAC reduction.

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Table 1. Schedule of Infusions^a

Dog	Dose 1	Dose 2	Dose 3	Dose 4
235	14.6/0.625	72/8	288/32	720/80
236	14.6/1.6	72/8	288/32	
237	14.6/1.6	72/8	288/32	720/80
238	14.6/1.6	72/8	288/32	720/80
239	14.6/1.6	72/8	288/32	720/80
240	14.6/1.6	72/8	288/32	720/80
241	14.6/1.6	72/8	288/32	720/80
261	14.6/0.625	14.6/1.6	288/32	720/80
262	14.6/0.625	14.6/1.6	288/32	720/80
263	14.6/0.625	14.6/1.6	288/32	720/80

^aPriming dose/maintenance infusion rate. The priming dose ($\mu\text{g}/\text{kg}$) was infused at a constant rate over 20 mins. The maintenance infusion rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was constant from the beginning to the end of each dose period and was in addition to the priming dose.

Methods

The protocol was approved by the Emory University Animal Use and Care Committee and followed guidelines established by the National Institutes of Health for the ethical use of animals for research studies.

Hydrated fasting mongrel dogs ($n = 10$) of either sex weighing 15.7 ± 1.0 kg (all results expressed as the mean $\pm$ SEM) were each given IV succinylcholine (0.13 ± 0.01 mg/kg) and atropine (0.12 ± 0.01 mg/kg). Anesthesia was immediately induced with 5% enflurane in oxygen delivered by a Bain anesthesia circuit and a specialized mask (12). A cuffed endotracheal tube was introduced and ventilation with a Harvard respirator maintained arterial blood gases in the normal range. An intravenous catheter was inserted into a foreleg vein and lactated Ringer's solution was infused at a rate of 12.3 ± 0.5 ml $\cdot$ kg $^{-1}\cdot$ hr $^{-1}$. A urinary catheter was inserted and the tail shaved. Temperature was monitored using an esophageal temperature probe and maintained within 1.5°C over the course of the anesthetic (9.1 ± 0.3 hr) by the use of a warming blanket. The ECG was monitored throughout the experimental period. A femoral arterial cannula was utilized for continuous blood pressure recording, for periodic sampling of blood for gas analysis, and for the determination of alfentanil concentration in plasma. End-tidal enflurane concentration was measured by a Beckman LB-2 infrared analyzer. MAC determinations using the tail-clamp method were made as previously described for similar experiments from this laboratory (3). MAC was defined as that end-tidal enflurane concentration to the nearest 0.1% midway between the end-tidal concentrations of enflurane at which the dog did or did not move in response to the stimulus. After determination of the control enflurane MAC, each dog received alfentanil (all doses expressed as the base) in a series of increas-

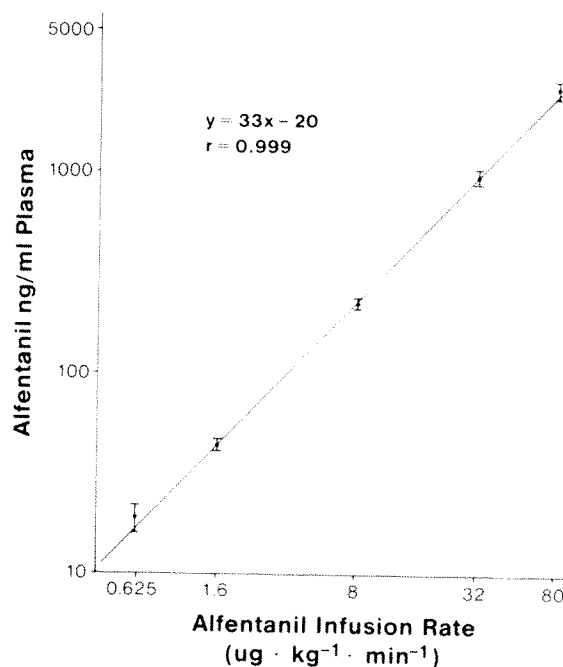


Figure 1. Alfentanil concentration in plasma (log scale) vs maintenance infusion rate (log scale). Each point represents the mean ($\pm$ SEM) concentration of alfentanil measured over the period during which MAC was determined and plasma concentrations were maintained at a stable level.

ing infusion rates (Table 1). The approach to stable alfentanil concentrations in plasma was hastened by a priming infusion administered over 20 min and simultaneously starting the maintenance infusion that was kept at a constant rate (13). At the end of a 1-hr period during which plasma concentrations of alfentanil stabilized, MAC determinations were repeated. With one exception, each dog received at least four different infusion rates. Arterial blood samples for measurement of plasma alfentanil concentrations were obtained 45 min after the start of each new infusion rate and then every 15 min until the determination of MAC was completed for each of the infusion rates. Equal volumes of 5% albumin were used to replace blood lost through sampling.

The alfentanil concentration in plasma was determined by radioimmunoassay (within assay variation 2.9%; between assay variation 5.3%) (14). Linear regression analysis was performed to determine the slope of the line representing the plasma concentration vs infusion rate of alfentanil. Student's *t*-test was used to determine if enflurane MAC during the initial alfentanil dose-rate differed from control. A one-way analysis of variance was used to identify dose-rate-related and concentration-related differences in degree of MAC reduction. $P < 0.05$ was taken as statistically significant.

Table 2. Enflurane MAC Reduction (%) and Plasma Alfentanil Concentrations (ng/ml) Produced by Incremental Increases in Alfentanil Infusion Rates

Maintenance infusion rate ^a ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	<i>n</i> ^b	End-tidal enflurane (% end-tidal gas)	Reduction of enflurane MAC (%, mean $\pm$ SEM)	Alfentanil (ng/ml plasma)
Control	10	2.37 $\pm$ 0.10	0	0
0.625	4	1.93 $\pm$ 0.25	24.1 $\pm$ 4.7 ^c	19 $\pm$ 3
1.6	9	1.15 $\pm$ 0.15	52.9 $\pm$ 5.8 ^c	44 $\pm$ 3
8.0	7	0.77 $\pm$ 0.13	68.5 $\pm$ 6.0 ^c	223 $\pm$ 13
32.0	10	0.69 $\pm$ 0.10	72.5 $\pm$ 3.7 ^{c,d}	960 $\pm$ 86
80.0	9	0.74 $\pm$ 0.08	70.3 $\pm$ 2.4 ^{c,d}	2613 $\pm$ 247

^aThis is the constant infusion rate maintaining stable alfentanil concentrations in plasma during the determination of MAC. The dogs had already received a priming infusion as indicated in Table 1.

^bNumber of dogs studied at each of the maintenance infusion rates listed in column 1.

^c $P < 0.05$ vs control.

^d $P < 0.05$ vs that produced by an infusion rate of $1.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$.

Results

Incremental increases in alfentanil infusion rates produced proportional increases in plasma alfentanil concentrations ($r = 0.999$; Fig. 1; Table 2). The mean plasma alfentanil concentration of 19 ± 3 ng/ml at an infusion rate of $0.625 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ produced a $24.1 \pm 4.7\%$ reduction of enflurane MAC. Higher concentrations produced greater reductions of enflurane MAC, but a ceiling effect was evident (Fig. 2). The maximum MAC reduction of $72.5 \pm 3.7\%$ at a plasma alfentanil concentration of 960 ± 86 ng/ml and an infusion rate of $32 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was not statistically different from the $68.5 \pm 6.0\%$ reduction produced by a plasma concentration of 223 ± 13 ng/ml at an infusion rate of $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$.

One dog (No. 236, Table 1) achieved a 92.9% reduction of enflurane MAC at an infusion rate of $32 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ with stable alfentanil concentrations of 555 ± 29 ng/ml. In this dog, a plasma concentration of 240 ± 12 ng/ml produced by a maintenance infusion rate of $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ decreased enflurane MAC by 50.2% vs an average enflurane MAC reduction of $52.9 \pm 5.8\%$ produced by an alfentanil concentration of 44 ± 3 ng/ml plasma (Table 2). In other words, in this particular dog, alfentanil appeared to be less potent (higher concentrations required to produce equivalent degrees of anesthetic effect) but more efficacious (able to replace enflurane MAC by 92.9%) than in the other nine dogs.

Discussion

This study in dogs and that of Ausems et al. (2) in human patients provide for the first time data on the plasma concentration vs anesthetic effect relationships by which the anesthetic efficacy of an intravenous opioid can be directly compared in humans and

dogs. In the present study of dogs, an alfentanil concentration of 223 ng/ml of plasma combined with enflurane 0.77% (33% MAC) in end-tidal gas (total = 1 MAC) obtunded the movement response to a tail-clamp stimulus. In humans, Ausems et al. (2) demonstrated that, under precise experimental conditions, 279 ng/ml alfentanil + 66% nitrous oxide (63% MAC) (total = 1 MAC) was required to prevent somatic (i.e., movement) and hemodynamic responses in 50% of patients to a surgical skin incision. Surgical skin incision in humans is considered to be the MAC-equivalent stimulus to tail-clamping in dog (11). Thus, it appears that the plasma concentrations of alfentanil required to produce equivalent anesthetic effects in humans and dogs are similar.

Data from other studies are suggestive of similar anesthetic efficacies for opioids in humans and dogs. In patients receiving fentanyl anesthesia for coronary artery bypass grafting, Sprigge et al. observed that after a morphine, scopolamine, and diazepam premedication, hemodynamic responses to different surgical stimuli were attenuated in approximately 50% of patients by plasma fentanyl concentrations of 15–18 ng/ml and plasma fentanyl concentrations of 30 ng/ml suppressed approximately 90% of responses (15). In the dog, 50% reduction of enflurane MAC occurred at a plasma fentanyl concentration of approximately 5 ng/ml and the maximal degree of MAC reduction (65%) occurred at fentanyl concentrations in the range of 10–30 ng/ml plasma (3). Philbin et al., utilizing a morphine, scopolamine, diazepam premedication, were unable to prevent some hemodynamic responses and elevations in plasma catecholamine levels with plasma sufentanil concentrations from 3 to 55 ng/ml in patients undergoing coronary artery bypass grafting surgery (16). In the dog, plasma concentrations above 2 ng/ml failed to produce greater than 70% reduction of enflurane MAC (8).

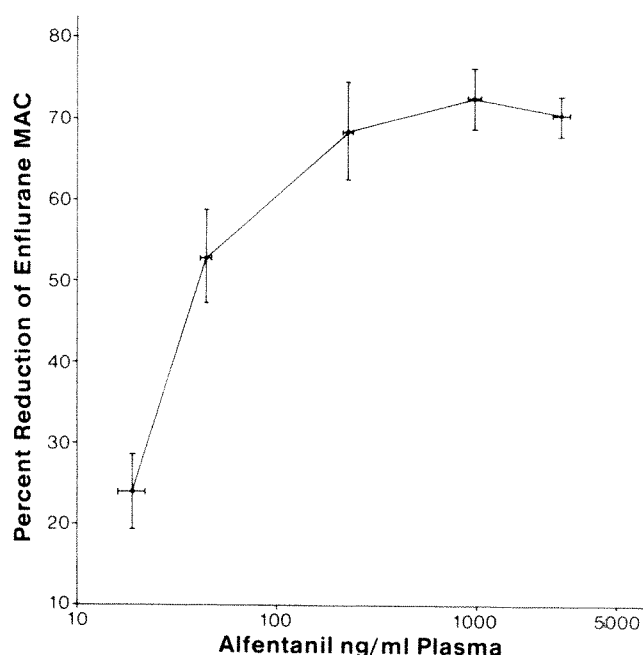


Figure 2. Alfentanil concentration in plasma (log scale) vs percentage reduction of enflurane MAC. Each point represents the mean ($\pm$ SEM) reduction in enflurane MAC produced by a stable plasma concentration of alfentanil (ng/ml $\pm$ SEM) maintained by a continuous infusion.

Our experiments show that the degree of MAC reduction produced by opioid analgesics in the dog is finite and is based on pharmacodynamic considerations rather than on pharmacokinetic ones. That this may also be true in humans is supported by the observation in patients that in the presence of a low dose of lorazepam premedication (0.04 mg/kg) alfentanil concentrations in the range of 2000–3000 ng/ml plasma proved insufficient to maintain anesthesia adequate for coronary artery bypass operations. Increasing the lorazepam premedicant dose to 0.08 mg/kg enabled alfentanil to serve as a satisfactory anesthetic agent at plasma concentrations of 1000–1500 ng/ml (17,18).

The maximal degree of enflurane MAC reduction (69% at 223 ng/ml) is not unlike the maximal effect of fentanyl (65% at 30 ng/ml) (3). However, one dog in the present study achieved 93% MAC reduction at a plasma concentration of 555 ng/ml. We can only speculate that this may represent biological variation within the species.

Lake et al. examined the ability of alfentanil to reduce halothane MAC in the rat and found that a dose of $15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ produced a 48% reduction of halothane MAC (7). This was achieved at a plasma concentration of 100 ng/ml. In dogs we observed a 53% reduction of enflurane MAC at a plasma con-

centration of 44 ± 3 ng/ml. Thus, it appears that the dog is slightly more sensitive to alfentanil than the rat. It should be noted, however, that their study (7) was hampered by the development of chest wall rigidity and difficulty ventilating the rat and the resultant changes in physiology preclude precise comparison of their data to ours. Chest wall rigidity is not a feature of narcotic administration in the dog anesthetized with enflurane.

In terms of the plasma concentrations associated with equivalent degrees of MAC reduction in the dog, alfentanil was approximately one-seventh to one-tenth as potent as was fentanyl. That is, a 50% reduction in enflurane MAC would be expected with a plasma alfentanil concentration of approximately 54 ng/ml or a plasma fentanyl concentration of 5.2 ng/ml (10:1) and maximal MAC reduction at plasma concentrations of 223 vs 20–30 ng/ml (10–7:1). [Compare Figure 2 in this manuscript to Figure 1 in the article by Murphy and Hug (3)]. This 7–10:1 potency ratio for equivalent anesthetic effect is similar to that based on dose and reported previously for animals (2–5:1) (1,19) and humans (4–6:1) for analgesic effect (1). It differs, however, from the 75:1 potency ratio for alfentanil vs fentanyl that was based on the EC₅₀ concentrations for shifting the spectral edge of the EEG in patients before surgery (20). A common observation is that patients rendered asleep or unconscious before surgical stimulation often respond with movement or hemodynamic changes at the time of surgical stimulation (e.g., skin incision). The dose/concentration requirement for loss of consciousness may differ from the requirement for suppression of responses to noxious stimulation (2). The present data in dogs, taken together with the results reported by Ausems et al. (2) and Scott et al. (20), suggest that whenever relative potencies of opioids are compared, the stimulus against which the comparison is made must be clearly defined.

We conclude that alfentanil, like other opioid analgesics, is capable of reducing enflurane MAC by only 70% in dogs. Studied under identical conditions, alfentanil is one-seventh to one-tenth as potent as fentanyl. The anesthetic efficacy of alfentanil in humans and dogs appear to be similar.

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Mechanisms of Succinylcholine-Induced Arrhythmias in Hypoxic or Hypoxic:Hypercarbic Dogs

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LEIMAN BC, KATZ J, BUTLER BD. Mechanisms of succinylcholine-induced arrhythmias in hypoxic or hypoxic:hypercarbic dogs. *Anesth Analg* 1987;66:1292-7.

To evaluate the effects of succinylcholine on cardiac arrhythmias and serum levels of potassium and catecholamines, dogs with hypoxia alone and with hypoxia and hypercarbia were studied during anesthesia with halothane or enflurane. After the injection of succinylcholine (0.3 mg/kg), cardiac arrhythmias occurred in all halothane: hypoxia dogs and in 70% of dogs given halothane during hypoxia: hypercarbia. No dogs given enflurane anesthesia developed arrhythmias. Serum potassium levels increased significantly 3 and 5 min after succinylcholine in all groups. Serum epinephrine levels increased in the halothane-hypoxia: hypercarbia and enflurane: hypoxia groups and, after the in-

jection of succinylcholine, epinephrine levels increased further in dogs in the halothane: control, halothane: hypoxia, halothane-hypoxia: hypercarbia, enflurane: hypoxia, and enflurane-hypoxia: hypercarbia groups. Norepinephrine levels increased with enflurane-hypoxia: hypercarbia and after the succinylcholine in the halothane: hypoxia, halothane-hypoxia: hypercarbia, and enflurane-hypoxia: hypercarbia groups. The results suggest that succinylcholine induces arrhythmias by sympathetic stimulation and that halothane sensitizes the myocardium to arrhythmias at the same levels of serum catecholamines and potassium in the presence of hypoxia or hypoxia: hypercarbia more than does enflurane.

Key Words: NEUROMUSCULAR RELAXANTS—SUCCINYLCHOLINE. HEART—arrhythmias. HYPOXIA. CARBON DIOXIDE—hypercarbia.

Succinylcholine is useful before tracheal intubation because of the rapid onset of profound muscle relaxation it provides. In situations in which intubation may be difficult and delayed, patients may be hypoxic as well as hypercarbic and acidotic. The safety of succinylcholine in such a situation may be questioned because of the potential development of cardiac arrhythmias, including sinus bradycardia (1-3), junctional rhythms, and ventricular arrhythmias (3) that may be exacerbated by hypoxia and acidosis. Ventricular arrhythmias have been attributed to the release of potassium from skeletal muscle (4,5), which succinylcholine certainly does. Acidosis is also associated with the development of hyperkalemia, which may be further accentuated by succinylcholine.

It has been speculated that succinylcholine stimulates both nicotinic receptors of sympathetic ganglia as well as postganglionic sympathetic terminals (6).

Nicotinic agonists that stimulate these receptors produce a dramatic release of norepinephrine (7). Furthermore, the injection of succinylcholine in humans increases serum levels of both epinephrine and norepinephrine, with peak levels of epinephrine reached at 2 min and of norepinephrine at 3 min (6).

To determine the effects of succinylcholine on cardiac rhythm and serum levels of potassium and catecholamines, we established a dog model using halothane (to provide a sensitized myocardium) or enflurane anesthesia, in which a state of hypoxia with or without respiratory acidosis was present.

Methods

Surgery

Anesthesia was induced in healthy dogs with thiopental (25 mg/kg), the trachea intubated, and anesthesia maintained with halothane 1.0% or enflurane 2.5% in the inspired air. The dogs were ventilated (Harvard) with oxygen and nitrogen using an intermittent mandatory ventilatory circuit that permitted them to take spontaneous breaths. Inspired gas tensions were controlled with the aid of a mass spec-

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Table 1. Blood Gas Data

		Baseline	Before succinylcholine injection
Halothane: hypoxia ($n = 10$)	PaO ₂ (mm Hg)	118 ± 9.2 ^a	29 ± 1.5 ^b
	PaCO ₂ (mm Hg)	35 ± 1.5	33 ± 0.9
Halothane-hypoxia: hypercarbia ($n = 10$)	PaO ₂ (mm Hg)	128 ± 11	26 ± 1.1 ^b
	PaCO ₂ (mm Hg)	33 ± 1.3	73 ± 3.3 ^b
Enflurane: hypoxia ($n = 10$)	PaO ₂ (mm Hg)	127 ± 7	26 ± 1.2 ^b
	PaCO ₂ (mm Hg)	36 ± 2	36 ± 1.3
Enflurane-hypoxia: hypercarbia ($n = 8$)	PaO ₂ (mm Hg)	120 ± 10	27 ± 1.1 ^b
	PaCO ₂ (mm Hg)	36 ± 2.1	71 ± 3.3 ^b

^aData are mean ± SE.^bSignificantly different ($P < 0.05$) from baseline (normoxia).

trometer (Perkin-Elmer) to maintain an FI_{O₂} of 0.25 during the baseline period.

Arterial blood pressure (BP) was measured with an abdominal aortic catheter placed via the right femoral artery, left ventricular end-diastolic pressure (LVEDP) with a catheter in the left ventricle via the right carotid artery, and pulmonary arterial pressures and thermodilution cardiac output (Instrumentation Laboratories) with a balloon-tipped pulmonary artery catheter (Instrumentation Laboratories) placed via the right jugular vein. Cardiac output was taken as the mean of three consecutive readings. A second arterial catheter was placed in the left femoral artery to obtain blood for measurements of blood gas tensions and plasma levels of potassium and catecholamines. A catheter was inserted in the femoral vein for fluid administration and the injection of succinylcholine. The pressure-monitoring catheters were connected to strain gauge transducers (Statham, P23ID), zero-referenced at the right atrial level, and calibrated with a mercury column. Data were recorded on a strip chart recorder (Gould). Continuous ECG monitoring from leads II and/or V₅ was used for the detection of arrhythmias and myocardial ischemia. Baseline data were collected after a 30-min stabilization period.

Arterial blood samples for measurement of potassium and catecholamine levels were collected before and during hypoxia with normocarbida or hypoxia with hypercarbia before succinylcholine injection and for measurement of potassium levels every minute for 5 min and for catecholamine measurement 3 min after the injection of succinylcholine. Potassium levels were determined from whole blood samples using an ion-specific Na⁺/K⁺ analyzer (Instrumentation Laboratories).

For catecholamine analysis, the serum obtained from arterial blood samples was stabilized with sodium metabisulfite and frozen to -70°C for future analysis. Samples were analyzed using high-pressure liquid chromatography (Waters Associates) with peak val-

ues determined using a Hewlett-Packard integrator. Reagent preparation and catecholamine elution using alumina extraction are further described by Keller et al. (8).

Hypoxia, Hypoxia and Hypercarbia

After the collection of baseline (normoxia) data, hypoxia and hypercarbia were induced by adjusting the oxygen, nitrogen, and carbon dioxide concentrations delivered to the ventilatory circuit. Gutierrez et al. (9) have shown that when PaO₂ decreases to 20–30 mm Hg, there is an initial increase in oxygen uptake followed by a decrease thereafter. In this study an FI_{O₂} = 0.09 was required to obtain a PaO₂ of between 21 and 36 mm Hg (Table 1). An FI_{CO₂} of about 0.09 was required to achieve a PaCO₂ between 60 and 72 mm Hg. Blood gas tensions were measured at 5-min intervals (Instrumentation Laboratories) until the desired level of hypoxia was achieved and, in the hypercarbic groups, until PaCO₂ values of 60 mm Hg were reached. When the stable hypoxic or hypoxic: hypercarbic state had been established, succinylcholine 0.3 mg/kg was injected as a bolus dose. There are variations in the recommended dose and duration of action of succinylcholine (10). This dose is associated with a mean time of 25 min for spontaneous 50% recovery of muscle activity (11).

Experimental Groups

The dogs were randomly classified into four experimental and two control groups: Group 1, hypoxia with halothane (ten dogs); Group 2, hypoxia:hypercarbia with halothane (ten dogs); Group 3, hypoxia with enflurane (ten dogs); and Group 4, hypoxia:hypercarbia with enflurane (eight dogs). The two control groups were: C1, normoxia:normocarbida with halothane (five dogs); and C2, normoxia: normocarbida with enflurane (five dogs). After the experiments, two dogs

Table 2. Incidence of Arrhythmias after Succinylcholine Injections^a

	Bradycardia ^b (%)	Ventricular premature beats (%)	Ventricular tachycardia ^c (%)	Nodal tachycardia (%)	Total incidence of arrhythmias (%)
Halothane alone (<i>n</i> = 5)	0	0	0	0	0
Halothane with hypoxia (<i>n</i> = 10)	20	90	30	0	100 ^d
Halothane with hypoxia and hypercarbia (<i>n</i> = 10)	0	70	40	10	70 ^d
Enflurane alone (<i>n</i> = 5)	0	0	0	0	0
Enflurane with hypoxia (<i>n</i> = 10)	0	0	0	0	0
Enflurane with hypoxia and hypercarbia (<i>n</i> = 8)	0	0	0	0	0

^aValues are percentages of arrhythmias per number of dogs in each group.^bBradycardia: decrease in heart rate of greater than 30% from control.^cVentricular tachycardia: three or more ventricular premature beats in a row.^d*P* < 0.01 comparing halothane to enflurane total incidence.

from each group were monitored for an additional 30 min during hypoxia or hypoxia:hypercarbia.

Data Analysis

Physiologic and analytic data are expressed as means $\pm$ SE. The data in Table 1 were analyzed for statistical significance with the Student's *t*-test; *P* < 0.05 was considered significant. Fisher's exact tests were used to compare incidence of arrhythmias in Table 2. Two-way analysis of variance with the Bonferroni method of multiple comparison was used to evaluate the potassium, catecholamine, and cardiovascular data.

Results

Arrhythmias

The type and incidence of arrhythmias after succinylcholine are shown in Table 2. Four types of arrhythmias were recorded: bradycardia (decrease in heart rate greater than 30% from control), ventricular premature beats, ventricular tachycardia (three or more ventricular premature beats in a row), and nodal tachycardia. There were no arrhythmias detected during the collection of baseline samples. In the halothane:hypoxia group, all dogs developed arrhythmias, with ventricular premature beats being the most frequent (70%). In the halothane-hypoxia:hypercarbia group, seven of the ten dogs developed arrhythmias, with ventricular premature beats being the most frequent. No dog anesthetized with enflurane had any arrhythmias and there were no arrhythmias in the halothane control group. The incidence of arrhythmias was significantly greater for the halothane anesthetized dogs when compared to enflurane.

Catecholamines

The catecholamine data are shown in Table 3. In the halothane control group, serum norepinephrine levels decreased from 0.71 ± 0.4 to 0.42 ± 0.24 ng/ml (not significant) after the injection of succinylcholine, whereas the serum epinephrine levels increased significantly from 0.47 ± 0.2 to 1.43 ± 0.37 ng/ml.

In the enflurane control groups, there were no significant changes in norepinephrine levels after the injection of succinylcholine (0.53 ± 0.37 and 0.44 ± 0.32 ng/ml, respectively) or in epinephrine levels (0.37 ± 0.12 and 0.74 ± 0.32 ng/ml, respectively). In the halothane: hypoxia group, the norepinephrine and epinephrine levels did not change significantly. There were, however, significant increases in norepinephrine levels (to 1.38 ± 0.5 ng/ml) and in epinephrine levels (to 2.63 ± 0.59 ng/ml) 3 min after the succinylcholine injection.

In the halothane-hypoxia:hypercarbia group, the norepinephrine level did not change from baseline levels before succinylcholine was given, but after succinylcholine, norepinephrine levels increased significantly. Epinephrine levels increased significantly above baseline levels (to 1.14 ± 0.55 from 0.34 ± 0.1 ng/ml) during hypoxia:hypercarbia before succinylcholine and further increased to 2.31 ± 1 ng/ml after succinylcholine.

In the enflurane:hypoxia group, norepinephrine levels did not change significantly after the introduction of hypoxia or after succinylcholine. The epinephrine levels, however, increased above baseline levels of 0.36 ± 0.12 to 0.68 ± 0.11 ng/ml followed by a further significant increase after the succinylcholine to 1.18 ± 0.45 ng/ml.

In dogs anesthetized with enflurane and subjected to hypoxia and hypercarbia, epinephrine levels did not change significantly during hypoxia and hyper-

Table 3. Serum Catecholamine Levels

	Baseline (ng/ml)		Before succinylcholine injection (ng/ml)		After succinylcholine injection ^b (ng/ml)	
	Norepi ^a	Epi	Norepi	Epi	Norepi	Epi
Halothane alone (n = 5)			0.71 ± 0.40 ^c	0.47 ± 0.20	0.42 ± 0.24	1.43 ± 0.37 ^d
Halothane with hypoxia (n = 5)	0.46 ± 0.10	0.61 ± 0.32	0.76 ± 0.26	1.12 ± 0.50	1.38 ± 0.50 ^c	2.63 ± 0.59 ^{d,e}
Halothane with hypoxia and hypercarbia (n = 5)	0.31 ± 0.14	0.34 ± 0.10	0.77 ± 0.17	1.14 ± 0.55 ^f	1.41 ± 0.50 ^{d,e}	2.31 ± 1.0 ^{d,e}
Enflurane alone (n = 5)			0.53 ± 0.37	0.37 ± 0.12	0.44 ± 0.32	0.74 ± 0.32
Enflurane with hypoxia (n = 5)	0.75 ± 0.38	0.36 ± 0.12	0.50 ± 0.24	0.68 ± 0.11	0.97 ± 0.44	1.18 ± 0.45 ^{d,e}
Enflurane with hypoxia and hypercarbia (n = 5)	0.31 ± 0.16	0.85 ± 0.24	1.44 ± 0.36 ^f	1.28 ± 0.19	1.99 ± 0.73 ^c	4.1 ± 4.3 ^{d,e}

^aAbbreviations: Norepi, norepinephrine; Epi, epinephrine.^bSample collected 3 min after succinylcholine injection.^cData are mean ± SE.^dP < 0.05 comparing postsuccinylcholine and presuccinylcholine levels.^eP < 0.05 comparing postsuccinylcholine and baseline levels.^fP < 0.05 comparing presuccinylcholine and baseline levels.

carbia but increased significantly to 4.1 ± 4.3 ng/ml after succinylcholine. Norepinephrine levels increased from a baseline of 0.31 ± 0.16 to 1.44 ± 0.36 ng/ml at hypoxia:hypercarbia and then increased further to 1.99 ± 0.73 ng/ml after succinylcholine.

Serum Potassium

The serum potassium data are shown in Table 4. There were no changes from baseline levels before succinylcholine injection, but after succinylcholine, potassium levels were significantly increased at 3- and 5-min intervals. There were no intergroup differences.

Hemodynamics

Blood pressure, heart rate, cardiac output, and LVEDP remained unchanged from baseline after the introduction of hypoxia or hypoxia:hypercarbia with either halothane or enflurane. Pulmonary artery pressure and pulmonary vascular resistance increased with hypoxia and hypoxia:hypercarbia and decreased with succinylcholine. The changes were similar with halothane and with enflurane. The two dogs from each group that were monitored for an additional 30 min after the experiments had no further hemodynamic changes.

Control Groups

In the two control groups (no hypoxia or hypoxia:hypercarbia) there were no hemodynamic changes.

There were also no significant changes in serum potassium levels after succinylcholine with either halothane or enflurane.

Discussion

Our results indicate that succinylcholine induces arrhythmias in hypoxic or hypoxic:hypercarbic dogs when anesthetized with halothane. However, under the same respiratory conditions, arrhythmias do not occur when enflurane is the anesthetic. To evaluate the possible mechanisms by which these arrhythmias are created, we measured changes in serum potassium and circulating catecholamine levels and found that both increased significantly.

Succinylcholine causes an efflux of potassium from skeletal muscle cells in dogs (12) and humans (13), an effect that has been implicated as a cause of ventricular arrhythmias (4,5). However, to conclude that changes in potassium alone are the sole cause of the arrhythmias is overly simplistic. Although serum potassium does increase after succinylcholine (Table 4), the increase in catecholamine levels may not only modify the effects of potassium but also affect the balance of the autonomic nervous system.

Succinylcholine stimulates presynaptic nicotinic receptors on the postganglionic sympathetic terminals, producing a sudden but brief release of norepinephrine. Most of this norepinephrine is removed by reuptake into neuronal and extraneuronal tissues so that the plasma levels merely reflect overflow (14,15). We

Table 4. Serum Potassium Levels

	Baseline (mEq K ⁺ /L)	Before succinylcholine injection (mEq K ⁺ /L)	After succinylcholine injection (mEq K ⁺ /L)	
			3 min ^{a,b}	5 min ^{a,b}
Halothane alone (<i>n</i> = 5)	3.7 ± 0.2 ^c	3.5 ± 0.2	4.0 ± 0.2	4.1 ± 0.2
Halothane with hypoxia (<i>n</i> = 10)	3.5 ± 0.1	3.6 ± 0.1	4.2 ± 0.2	4.4 ± 0.2
Halothane with hypoxia and hypercarbia (<i>n</i> = 10)	3.5 ± 0.1	3.6 ± 0.2	4.3 ± 0.2	4.6 ± 0.2
Enflurane alone (<i>n</i> = 5)	3.5 ± 0.1	3.4 ± 0.1	3.9 ± 0.2	3.9 ± 0.2
Enflurane with hypoxia (<i>n</i> = 10)	3.5 ± 0.2	3.4 ± 0.1	3.8 ± 0.2	4.0 ± 0.2
Enflurane with hypoxia and hypercarbia (<i>n</i> = 8)	3.5 ± 0.1	4.0 ± 0.2	4.6 ± 0.2	4.6 ± 0.2

^aSignificantly different from baseline levels.^bSignificantly different from presuccinylcholine injection levels.^cData are mean ± SE.

measured catecholamine levels 3 min after succinylcholine was given because washout from the tissues is needed before appearance of the (delayed) peak in levels of catecholamine in the plasma (6). Succinylcholine may also produce cardiac effects by stimulating the release of norepinephrine directly into the myocardium, and this locally released norepinephrine may not be accurately reflected by changes in plasma levels (16).

Circulating catecholamines, especially epinephrine, produce prolonged hypokalemia in both experimental animals (17-19) and in humans (20). Furthermore, the adverse hemodynamic effects of toxic doses of potassium given by infusion are ameliorated by catecholamines (21,22). The dogs in the present experiments had significant increases in norepinephrine and/or epinephrine (Table 3) during hypoxia alone and during hypoxia with hypercarbia. Therefore, before the succinylcholine injection, catecholamines were exerting an influence on potassium flux, and this influence would therefore increase after the succinylcholine injection when the circulating levels of both norepinephrine and epinephrine were further elevated.

Acetylcholine is the neurotransmitter at the nicotinic receptor on the preganglionic terminals of both the sympathetic and parasympathetic systems, whereas norepinephrine is the postganglionic (adrenergic) sympathetic neurotransmitter and acetylcholine, the postganglionic (muscarinic) parasympathetic neurotransmitter. The net physiologic effect depends on the balance of the two systems. Young children are deficient in nicotinic receptors, and succinylcholine produces muscarinic effects (bradyarrhythmias), whereas in adults, at least with a single dose of succinylcholine, sympathetic effects predominate (tachyarrhythmias) (16). In this study it seems likely that sympathetic stimulation is predominating. Further

study under the same conditions using adrenergic, ganglionic, or muscarinic blockade will elucidate the balance of the two systems.

Epinephrine mediates its arrhythmogenic effects by increasing automaticity of cardiac cells and by decreasing the ventricular fibrillatory threshold (23). Adverse effects of catecholamines are expected to be more pronounced in the presence of hypoxia, hypercarbia, and inhalational anesthetic agents that "sensitize" the myocardium (16). We selected halothane as an anesthetic agent because of its ability to sensitize the heart to the effects of catecholamines, whereas enflurane is associated with a "nonsensitized myocardium."

Cardiac arrhythmias occurred only in the halothane-anesthetized dogs. This suggests that "myocardial sensitization" by halothane created an environment in which the effects of catecholamines were accentuated. This is supported by the work of Tucker and Munson (24), who showed that the threshold arrhythmogenic dose of epinephrine in dogs anesthetized with halothane was markedly decreased by a preceding bolus injection of succinylcholine. They concluded that succinylcholine increases the arrhythmogenicity of epinephrine during halothane anesthesia. Catecholamine increases have also been demonstrated to occur in hypoxic and hypoxic:hypercarbic sheep (25).

This study suggests that the increase in serum potassium levels, although statistically significant, is not the sole cause of the arrhythmias associated with succinylcholine, but that stimulation of the autonomic nervous system by succinylcholine likely plays an important role. This interpretation of these findings raises an important clinical question. Anesthetic deaths in pediatric patients are often related to hypoxic episodes resulting from the loss of control of the airway (26). Halothane is the most popular inhalation agent

used for induction of anesthesia in children, and succinylcholine will undoubtedly continue to be used. Therefore, the three ingredients (halothane, hypoxia, and succinylcholine) for potentially lethal arrhythmias are sometimes present. Enflurane does not appear to have wide popularity, whereas the use of isoflurane for inhalation induction is associated with coughing and breath-holding (27). We conclude that enflurane offers protection against succinylcholine-induced arrhythmias in hypoxic and hypoxic:hypercarbic dogs, and in this respect may offer an advantage over the use of halothane.

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Central Nervous System Complications After 6000 Retrobulbar Blocks

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Six thousand consecutive patients in whom retrobulbar anesthesia was performed by an anesthesiologist before ophthalmic surgery were studied. Sixteen patients (1 in 375) developed signs and symptoms presumed to be caused by the direct spread of the local anesthetic agents to the central nervous system. These signs and symptoms ranged from drowsiness, blindness of the contralateral eye, abnormal shivering, or vomiting, through to respiratory depression, apnea, hemiplegia, aphasia, convulsions, unconsciousness,

and cardiopulmonary arrest. The severity of the symptoms was unrelated to the dose of anesthetic administered. The time of the onset of symptoms after the retrobulbar injection was variable (average 8 min, range 2 to 40 min). The possibility of a life-threatening complication occurring was rare (1 in 750) but unpredictable. The need for closely monitored anesthesia care of all patients having surgery under retrobulbar anesthesia is stressed.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—retrobulbar block. ANESTHESIA—ophthalmologic.

There are increasingly frequent reports of potentially life-threatening complications after retrobulbar injections of long-acting local anesthetic agents (1-9). The most common has been respiratory arrest, although a case of transient cardiac arrest has also been reported (10). Blindness in the contralateral eye (8,11,12), seizures, and other neurologic signs have also been reported (13). The present study was undertaken to establish the incidence and spectrum of signs and symptoms that might be expected to arise from the unintentional spread of the local anesthetic agents from the site of injection to the central nervous system during retrobulbar nerve blocks. The effect of using a different technique of retrobulbar block on the incidence of these complications was also studied.

Methods

All patients scheduled for ophthalmic surgery and selected for retrobulbar anesthesia administered by one of the anesthesiologists were included in this study. Patients were ASA categories 1 to 4. Each one was

evaluated by an anesthesiologist before surgery when appropriate premedication was prescribed. Atropine was not used in premedication. On arrival in the preoperative holding area an intravenous infusion of 5% dextrose in Ringer's lactate solution was started. All patients were monitored with a three-lead continuous ECG and an automatic blood pressure-measuring device. An attendant nurse observed and recorded respiration and vital signs before the block was given and at 5-min intervals thereafter. These observations continued for 30 min after surgery had been completed, when the patient was discharged from the recovery room.

Retrobulbar anesthesia was achieved by a standard percutaneous inferotemporal approach with the patient instructed to look upward and inward. After the first 2000 procedures this was modified so that the patient was instructed to look straight ahead or minimally upward. A sharp, 38-mm 25-gauge disposable needle was used with the bevel inserted upward in all but 100 cases in which a 23-gauge blunt-ended needle was used instead. A combination of 2 ml 2% lidocaine, 3 ml 0.5% bupivacaine, and 75 IU hyaluronidase was used in all but 100 anesthetics. In 50 of these 100 anesthetics, the hyaluronidase was omitted. In another 50, 0.5% bupivacaine was combined with 75 IU of hyaluronidase. The volume of the injectate varied between 2.5 and 5.0 ml depending on

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the size of the orbit and the degree of proptosis induced by the injection. Before injection negative pressure was applied to the syringe plunger to be certain that the tip of the needle was not in a blood vessel. Facial nerve block was achieved by a variety of extraorbital techniques using from 1.5 to 5.0 ml of a solution containing equal volumes of 0.5% bupivacaine and 2% lidocaine. Unsatisfactory blocks were supplemented by additional injections of local anesthetics as necessary.

Results

Various signs and symptoms were encountered in the 16 cases in which there appeared to be spread to the central nervous system of the local anesthetic solution (Table 1). Minor sequelae included transient changes in the level of consciousness, abnormal shivering, or uncontrollable nausea and vomiting. Amaurosis and partial akinesia of the contralateral eye was seen in two cases. Abnormal patterns of respiration suggesting selective midbrain involvement occasionally progressed to apnea lasting for a few minutes or longer. Other focal neurologic signs included aphasia, hemiplegia, and facial paralysis. When convulsions occurred they were predominantly unilateral.

Changes in pulse rate or blood pressure, usually bradycardia and hypotension, were often the first changes to be noticed. The most serious complication in the series was a case of prolonged cardiac arrest. In this patient bradycardia rapidly progressing to asystole occurred within a few minutes of the retrobulbar anesthetic being injected. Tracheal intubation, ventilation, cardiac massage, and resuscitation drug therapy were required, during which a variety of dysrhythmias was encountered. Episodes of ventricular tachycardia with no cardiac output was treated twice by defibrillation. Cardiopulmonary resuscitation was sustained for a period of 45 min before the patient recovered.

Eleven different anesthesiologists participated in the study. Six of the 11 had patients in whom symptoms of central spread of local anesthetic developed. The number of retrobulbar anesthetics administered by each anesthesiologist varied between 55 and 1258, and the incidence of reactions ranged between 1 in 251 to 1 in 983.

After the first 2000 retrobulbar anesthetics had been given, a modified technique was used. The next 3370 blocks were performed with only three incidents of central spread, but there then followed a 2-week period when seven instances of central reaction occurred in 200 blocks. There was no demonstrable correlation between the experience of the anesthesiologist and

the incidence of complications. There was no change in technique, batch of agents used, nor anesthesiologist to account for this change in incidence rate. Overall there was no significant difference between the two techniques in the incidence of central spread.

The axial length of the eyeball in which complications of central spread occurred (mean, 23.79 mm) was similar to the axial length of 50 control patients (mean, 23.65 mm).

The postoperative records were studied for visual outcome in 13 of the 16 patients described. (Three patients were lost to follow-up.) In none of the 13 patients was there clinical evidence of optic nerve damage occurring after the retrobulbar injection.

Discussion

From the variety of signs and symptoms encountered it seems that when discrete quantities of the local anesthetic mixtures injected into the retrobulbar space spread to the central nervous system, they do so by spreading in a cephalad direction to anesthetize specific areas of the central nervous system. The most likely pathway for this spread is under the dural sheath of the optic nerve. The patency of this pathway has been demonstrated by contrast radiography (14) and by recovery of lidocaine and bupivacaine from the cerebrospinal fluid of patients who developed respiratory arrest subsequent to retrobulbar block (15). Blindness with paralysis of the third and sixth cranial nerve in the contralateral eye was seen in two cases. This phenomenon can best be explained by the anesthetic entering beneath the optic nerve sheath and passing via the optic chiasma to the midbrain. It is probable that this occurred more times than we describe but was neither looked for nor could be demonstrated in the unconscious or monocular patient.

In some but not all of the cases described, the anesthesiologist experienced a greater resistance on first attempts to inject the retrobulbar anesthetic, such as might be expected if the needle had entered the sheath of the optic nerve. When this change of resistance was felt the needle was withdrawn, but it seems that even a minute amount of the anesthetic misplaced into the subdural space was sufficient to give rise to symptoms of spread to the central nervous system.

Retrograde vascular spread along the ophthalmic artery and then anterograde in the internal carotid artery has been suggested as a possible explanation for high brain concentrations of anesthetic after retrobulbar blocks (10). Symptoms of central nervous system involvement from this route could be expected to follow almost instantaneously after the injection was given. It is very unlikely that the ophthalmic artery

Table 1. Case History Summary: Signs and Symptoms after Central Spread of the Local Anesthetic after Retrobulbar Block

Case No.	Series No.	Age (yr)	Sex	Time to Onset (min)	Side	Predominant signs and symptoms			Outcome ^a
						Circulatory	Respiratory	Neurological	
1	680	70	M	5	L	Hypertension, tachycardia	Depression	Aphasia, facial paresis	Surgery canceled, lost to follow-up
2	689	55	M	17	R	Hypotension	Depression, apnea	Comatose	Surgery canceled, GA later
3	1550	68	M	40	L	Hypotension, bradycardia	Depression	Semicomatose, contralateral amaurosis	Surgery proceeded under LA
4	1622	70	M	20	R	Bradycardia	—	Shivering	Surgery proceeded under LA
5	1671	60	M	2	L	—	—	Shivering	Surgery proceeded under GA
6	1871	50	F	6	R	Hypertension, bradycardia	Apnea after 12 min	Confusion, aphasia, convulsion after 14 min	Surgery proceeded under GA, uneventful recovery
7	2774	60	F	7	L	Bradycardia	Apneic for 2 min	Comatose	Surgery proceeded under LA
8	3709	55	M	5	R	Hypotension, bradycardia	Apneic for 10 min	Semicomatose, somnolent 2–3 hr	Surgery canceled, lost to follow-up
9	3880	46	F	2	R	Bradycardia, asystole, cardiac massage, ventricular tachycardia	Apneic for 45 min	Convulsions	Uneventful recovery, did not return for surgery
10	5371	67	F	4	R	Bradycardia	Apnea	—	Surgery canceled, GA later
11	5425	58	M	2	R	Chest pain	—	Shivering	Surgery proceeded with diazepam sedation and LA
12	5427	46	F	2	R	Hypotension, bradycardia	Apnea	Shivering, comatose	Surgery proceeded under GA, uneventful recovery
13	5448	67	M	2	R	Bradycardia	—	Nausea and vomiting (uncontrollable)	Surgery canceled, LA later
14	5459	60	M	3	L	—	Apnea	Semicomatose	Surgery canceled, GA later
15	5461	70	M	2	R	Hypotension, bradycardia	—	Shivering, semicomatose	Surgery proceeded under LA
16	5553	60	M	15	L	Hypotension, bradycardia	Depressed	Diaphoretic, semicomatose, contralateral amaurosis, IIIrd and VIth nerve palsy	Surgery proceeded under GA, uneventful recovery

^aAbbreviations: LA, local anesthesia; GA, general anesthesia.

could be cannulated on this number of occasions. Even if this were possible, signs of hemorrhage would have been expected. In none of the cases described was there evidence of hemorrhage or aspiration of blood into the syringe.

The total dosage of local anesthetic injected was a small fraction of the maximum recommended dose of each agent and therefore unlikely to cause systemic toxicity. Blood levels of the local anesthetics have been measured at intervals after respiratory arrest and compared with subjects in whom there was no abnormal response (6). No significant difference between the two groups was detected.

Long-acting local anesthetics are known to be more cardiotoxic than equieffective quantities of shorter-acting agents (16,17). Much of this evidence has come from animal studies in which serum levels have been equated to the observed toxic effects on the myocardium (18-21). It is now appreciated that the cardiotoxicity of local anesthetics can be mediated via the central nervous system (22). Recently animal experiments have also shown that the direct application of local anesthetics to specific areas of the brain have a profound effect on myocardial function (23,24). Both these studies confirmed that bupivacaine, applied directly to the brain, had cardiotoxic effects that were more profound and more dangerous than those associated with lidocaine. The escape of the local anesthetic from the orbit to the central nervous system can produce similarly profound effects. In most of the cases that we describe there was hypotension and bradycardia, but prolonged refractory cardiac arrest occurred in one case. The effect of spread of local anesthetic to the central nervous system during retrobulbar block depends on the amount of local anesthetic spreading to the brain and the specific area of the brain to which it spreads.

The addition of potent long-acting local anesthetic agents to the retrobulbar block has the advantage of prolonging the duration of anesthesia and providing some postoperative analgesia. Against these obvious advantages must be weighed the increased cardiotoxicity of these agents. A compromise can be reached by diluting the bupivacaine with the less cardiotoxic lidocaine. Two milliliters of 2% lidocaine mixed with 3 ml of 0.5% bupivacaine reduces the strength of each to 0.8 and 0.3%, respectively. Onset of action should be more rapid with the lidocaine/bupivacaine mixture than with bupivacaine alone.

It has been suggested that hyaluronidase might enhance the central spread of the local anesthetic solutions during retrobulbar blocks and thus increase the risk of central toxicity (25). However, this complication has been reported after a retrobulbar injection

in which there was no hyaluronidase (8). As the value for improving efficacy of the block by the addition of hyaluronidase has been demonstrated it would, on present evidence, seem unjustified not to use it (25).

A blunt needle might be less likely to penetrate the optic nerve sheath, although there is a report of central spread occurring with this type of needle (8). Blunt-tipped needles were tried for 100 blocks, but insertion was more painful and traumatic. It was felt that the potential for tissue damage was greater and any theoretical advantage unproven. By consistently using the same-sized needle and syringe, the anesthesiologist becomes familiar with the specific resistance of the tissues that can be expected with normal placement of the retrobulbar injection. Alteration in the position of gaze from upward and inward to a straight ahead fixation should move the optic nerve away from the needle. After changing to this method, there followed a period when the instance of central spread was considerably reduced. It would have been easy to assume that the answer had been found by this maneuver. However, the rash of complications that subsequently was suddenly encountered indicates that this is not a foolproof technique and at best it can only reduce, not eliminate, the chance of spread to the central nervous system of local anesthetics injected retrobulbarly.

Bradycardia, diaphoresis, and hypotension, immediately following manipulation of the eyeball, can be readily explained by the oculocardiac reflex. A more delayed response might be caused by a vasovagal reaction. On several occasions these signs occurred after retrobulbar injection. From the similarity in time delay at which they occurred, it was thought that some of these responses might well have been caused by the same centrally mediated myocardial depression mechanism. This diagnosis of central spread can be positively confirmed by finding paresis of the extraocular muscles of the contralateral eye. However, the absence of this sign does not rule out this possibility.

In the 6000 retrobulbar blocks that we performed, life-threatening sequelae were rare. In most cases symptomatic treatment with atropine, oxygen, intravenous fluids, and the head-down (Trendelenburg) position was all that was necessary. If, after the patient's condition was stabilized, anesthesia was adequate then surgery proceeded. When prolonged respiratory arrest or convulsions occurred and endotracheal intubation was necessary, general anesthesia was substituted as a therapeutic intervention and surgery was usually allowed to proceed. However, if the anesthesia was not adequate by the time

the patient was stable it was considered preferable that elective surgery be deferred until another day. Typically old age and disease have impaired the resilience of these patients and to subject them again so soon to the potential risks of inducing another anesthetic, whether local or general, was considered unwise.

With the one exception of asystole, most cases of central spread, if recognized early and treated promptly, should be of little danger to the patient. Local anesthesia is often the preferable choice of anesthetic for old or sick patients. Perioperative morbidity is reduced. Costs are less. With careful monitoring by staff qualified to treat any of the sequelae that might be encountered, this is a safe and effective form of anesthesia for ophthalmic surgery.

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A Comparison of Clinical and Psychological Effects of Fentanyl and Nalbuphine in Ambulatory Gynecologic Patients

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GARFIELD JM, GARFIELD FB, PHILIP BK, EARLS F, ROAF E. A comparison of clinical and psychological effects of fentanyl and nalbuphine in ambulatory gynecologic patients. *Anesth Analg* 1987;66:1303-7.

Drug dosages, length of stay (LOS), and incidence of psychological side effects of fentanyl and nalbuphine were compared in a randomized, double-blind study using unpremedicated female day-surgery patients undergoing diagnostic laparoscopy. Patients received either fentanyl 1.5 µg/kg (F group; n = 142), low-dose nalbuphine 300 µg/kg (LN group; N = 103), or high-dose nalbuphine 500 µg/kg (HN group; n = 41), intravenously (IV) before anesthesia consisting of thiopental, N₂O, O₂, and a succinylcholine infusion. Additional IV intraoperative and IM postoperative opioids were given if required for signs of inadequate anesthesia or post-

operative pain. The patients' clinical and psychological status was evaluated at 20-min intervals postoperatively by a team of trained interviewers. The low- and high-dose nalbuphine groups clinically resembled the fentanyl group in terms of dosing frequency and patients' self-ratings of postoperative analgesia. Length of stay and postoperative sedation were significantly greater with nalbuphine. The incidence of psychological side effects, including dreaming and postoperative anxiety, was also greater with nalbuphine. However, patient acceptance of nalbuphine was high and was similar to that observed in patients given fentanyl.

Key Words: ANESTHESIA—out-patient. ANESTHETICS, INTRAVENOUS—fentanyl, nalbuphine. ANALGESICS—fentanyl, nalbuphine.

Nalbuphine is a mixed agonist-antagonist opioid with an analgesic duration of action of approximately 3-4 hs. In day-surgery patients having brief (30-45 min) procedures under general anesthesia, this 3-4 hr corresponds to the time between beginning of surgery and discharge from the day-surgery unit (DSU). We hypothesized that a single loading dose of nalbuphine, administered intravenously as the narcotic component of a balanced anesthetic technique in patients having a standard gynecologic procedure might result in effective analgesia throughout the entire time in the DSU, wearing off about the time most patients are ready for discharge. Fentanyl, on the other hand, is a short-acting opioid often given repeatedly postoperatively, thereby increasing the risk of respiratory depression. We attempted to determine whether there were significant differences between the two opioids

in length of stay in the DSU, in the incidence of nausea, analgesia, and threatening psychological side effects, as well as overall acceptability.

Methods

The cumulative number of drug doses, length of stay (LOS), and incidence of psychological side effects associated with the two opioids were compared in a randomized, double-blind study in 286 unpremedicated female day-surgery patients undergoing diagnostic laparoscopy under general anesthesia. The demographics of the study patient population appear in Table 1. Institutional approval was granted and written informed consent was obtained from all patients. Randomization was accomplished through a code maintained at the inpatient pharmacy where unit doses of study drugs were prepared. Blinding was accomplished by dilution of drug dosages to identical volumes in coded syringes. We considered the potency ratio between fentanyl and nalbuphine to be 200:1. Depending on group assignment, patients received either fentanyl 1.5 µg/kg (F group; n = 142), low-dose nalbuphine 300 µg/kg (LN group; n = 103), or high-dose nalbuphine 500 µg/kg (HN group; n = 41) as

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Table 1. Demographics^a

	Fentanyl (F) (n = 142)	Low nalbuphine (LN) (n = 103)	High nalbuphine (HN) (n = 41)
Age (yr $\pm$ SD)	30.7 $\pm$ 4.46	29.7 $\pm$ 4.93	31.2 $\pm$ 5.09
Body weight (kg $\pm$ SD)	60.0 $\pm$ 9.14	59.1 $\pm$ 7.96	60.5 $\pm$ 8.50
Race			
White	139 (97.9%)	99 (98.0%)	41 (100%)
Black	3 (2.1%)	2 (2.0%)	0 (0%)

^aThere are no significant differences among treatment groups for any of the variables.Table 2. Number of Supplementary Doses of Narcotics Administered^a

	Fentanyl (F) (n = 142)	Low nalbuphine (LN) (n = 103)	High nalbuphine (HN) (n = 41)
Number of intraoperative supplementary doses	1.06 $\pm$ 0.07 ^b	0.92 $\pm$ 0.08	1.15 $\pm$ 0.14
Number of postoperative doses	0.50 $\pm$ 0.07	0.63 $\pm$ 0.09	0.44 $\pm$ 0.14
Total number of supplementary doses (intraplus postoperative)	1.56 $\pm$ 0.10	1.55 $\pm$ 0.12	1.59 $\pm$ 0.22

^aThere are no significant differences among drug groups for any of the variables.^bValues are mean $\pm$ SEM.

initial loading dose components of balanced anesthesia consisting of thiopental, N₂O, and a succinylcholine infusion. Loading doses were given intravenously 4 min before induction and followed by 4 mg/kg dose of thiopental. In addition to induction dose, the anesthetist was also issued a second coded syringe containing a total of 2.25 μ g/kg fentanyl or 450 μ g/kg nalbuphine. He or she was instructed to inject one-third of its contents, e.g., 0.75 μ g/kg fentanyl or 150 μ g/kg nalbuphine intravenously as needed on development of signs of inadequate anesthesia, e.g., sweating, tachycardia, or hypertension in response to surgical stimulation.

Postoperatively, recovery room nurses were instructed to administer one-third a syringe intramuscularly according to their clinical judgment, as needed, when a patient developed pain of sufficient degree to warrant a narcotic. Thus, up to three postoperative doses each of 0.75 μ g/kg fentanyl or 150 μ g/kg nalbuphine could be given.

All patients were given the Nowliss and Nowliss Mood-Adjective Checklist (MACL) 1-2 days preoperatively when interviewed and recruited for the study and again on discharge from the DSU. Their clinical course was followed up at 20-min intervals during recovery by trained observers who were unaware of assigned drug groups. An open-ended interview on discharge from the DSU enabled classification and quantitation of subjective reactions, based on a prior study in which we compared patients' subjective psychological reactions to ketamine and thiopental-nitrous oxide-halothane anesthesia (1).

Initially, 205 patients were studied, 102 receiving fentanyl and 103 low-dose nalbuphine, i.e., a 300 μ g/kg induction dose. However, we learned that other institutions studying nalbuphine were using higher loading doses, i.e., 500-1200 μ g/kg for surgical procedures done with a balanced technique and had reported good results without untoward side effects or excessive sedation postoperatively (2). Accordingly, we increased the nalbuphine loading dose to 500 μ g/kg (HN group). Intraoperative supplementary doses and postoperative doses remained the same, i.e., 150 μ g/kg. This phase of the study included 40 fentanyl patients and 41 HN patients, a total *n* of 286. For data analysis, the patients given fentanyl were grouped together because their dosages were identical. Data analysis was performed using parametric and nonparametric statistical tests. *P* < 0.05 was considered statistically significant.

Results

Supplementary Dosing Frequencies:

The mean number of supplementary doses for each drug group intraoperatively and postoperatively is shown in Table 2. There were no significant differences among the three drug groups intraoperatively or postoperatively.

Clinical and Predicted Opioid Potencies

As shown in Table 3, the total dose in the LN group was 540.91 μ g/kg and in the F group, 2.69 μ g/kg. The

Table 3. Drug Dosages

	Fentanyl (F) (<i>n</i> = 142) ($\mu\text{g/kg}$)	Low nalbuphine (LN) (<i>n</i> = 103) ($\mu\text{g/kg}$)	High nalbuphine (HN) (<i>n</i> = 41) ($\mu\text{g/kg}$)
Intraoperative dosage (includes loading dose)	2.3 ± 0.06^a	440.9 ± 11.67	697.7 ± 22.16
Postoperative dosage	0.38 ± 0.05	100.0 ± 14.47	67.1 ± 21.71
Total	2.69 ± 0.08	540.9 ± 19.95	746.8 ± 33.26

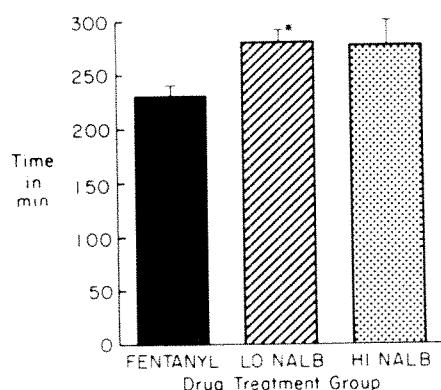
^aValues are mean $\pm$ SEM.

Figure 1. LOS data in each drug group. Drug groups are shown on the abscissa. Elapsed times in minutes $\pm$ SEM from entry into the recovery room until the IV was removed are shown on the ordinate. * $P < 0.05$ vs fentanyl.

ratio equals 201.32, almost identical to the predicted potencies. This does not hold true in the HN group, where the intraoperative dose alone exceeded total dose for the LN group.

Length of Stay (LOS)

There were no differences in duration of surgery among the three groups (mean $\pm$ SEM = 44.8 ± 1.4 min). Postoperative LOS, defined as the time from entry into the recovery room to removal of the IV in preparation for discharge is shown graphically in Figure 1. The difference between low nalbuphine and fentanyl groups was statistically significant. Five study patients, 1.7% of the total, required overnight admission to the hospital. These patients were regarded as outliers who did not complete the study and were not included in the LOS data. Of the five, four received nalbuphine, three with excessive disorientation and sedation. The fourth patient, who developed urticaria and wheezing of uncertain etiology, was admitted overnight for observation. One patient who received fentanyl was admitted for disorientation and persistent diplopia.

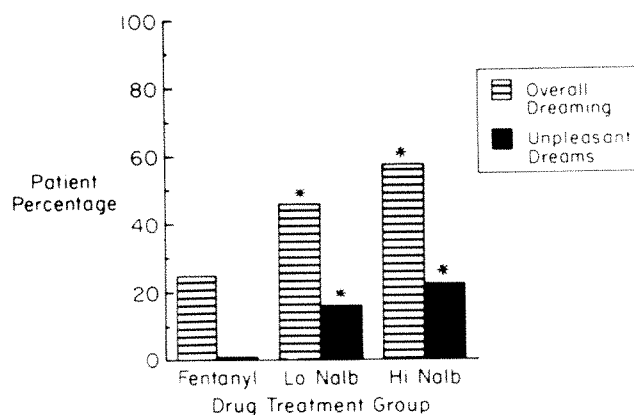


Figure 2. Incidence of dreaming of any type (overall dreaming) and unpleasant dreams. Drug treatment groups are shown on the abscissa. Patient percentages are shown on the ordinate. * $P < 0.05$ vs fentanyl.

Dreaming and Unpleasant Dreams

The incidence of dreaming of any type and of unpleasant dreams is shown in Figure 2. Patients in each of the two nalbuphine groups had a significantly higher incidence of dreaming during anesthesia and of unpleasant dreams during recovery than did patients in the fentanyl group. A dose-dependent relation is also suggested by the graphical data.

Postoperative Nausea

The incidence of postoperative nausea and the frequency of anti-emetic use in the three drug groups is shown in Figure 3. In the fentanyl group, the incidence of nausea was similar to that of other reports after diagnostic laparoscopy (3). Both nalbuphine groups had a significantly higher incidence of nausea than did the fentanyl group and there is a suggestion of a dose-effect relation. The frequency of use of hydroxyzine closely paralleled the incidence of nausea, in that almost everyone who became nauseated received hydroxyzine. If a patient failed to respond to two 50-mg IM doses of hydroxyzine, a 625- μg IM dose

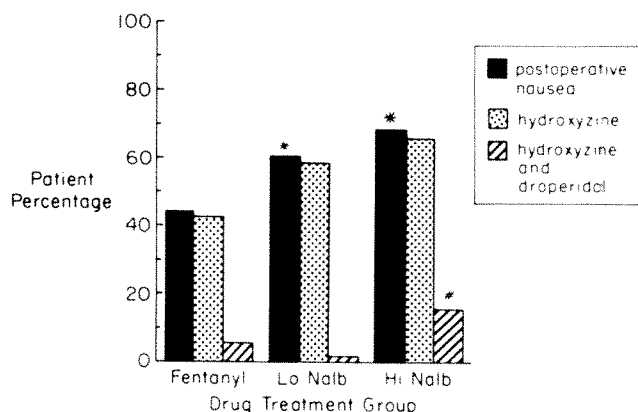


Figure 3. Frequency of postoperative nausea and use of antiemetics. Drug treatment groups are shown on the abscissa. Patient percentages are shown on the ordinate. * $P < 0.05$ vs fentanyl. # $P < 0.05$ vs low nalbuphine.

of droperidol was given. Note that the percentage of patients requiring droperidol was relatively low.

Anxiety

There were no preoperative differences in anxiety scores on the Nowliss and Nowliss Mood-Adjective Checklist (MACL) among the three drug groups. Postoperatively, the high nalbuphine group had a significantly higher score than the fentanyl group on the MACL, indicating a higher degree of anxiety at the time of discharge from the DSU.

Drowsiness and Lethargy

On discharge from the DSU, both the low nalbuphine and high nalbuphine groups had significantly higher scores on the MACL compared with preoperative control scores than did the fentanyl group.

Overall Postoperative Analgesic Efficacy

Immediately before discharge from the DSU, patients were asked to give an overall assessment of postoperative analgesia as "poor, fair, good, or excellent." These self-ratings were "good" or "excellent" in 83.6% of the cases (275 of 286 patients), with no significant differences among the three groups.

Satisfaction with Anesthesia

When asked what they would like to have done differently next time, only 5% of patients complained about aspects of their anesthesia, with no significant differences in the frequencies of anesthesia-related

complaints among drug groups. No patient specifically requested that a different opioid or different form of anesthesia be used in the future.

Discussion

Our hypothesis was that a single loading dose of nalbuphine at induction of anesthesia would be sufficient not only for the operation, but would continue to provide adequate postoperative analgesia over the additional 2-3 hr before time of discharge. This did not prove to be true. In fact, anesthesiologists and recovery room nurses treated the three drug groups identically, in that each group received the same number of additional doses both intraoperatively and postoperatively (Tables 2 and 3). The number of supplementary doses of narcotics in the fentanyl and low nalbuphine groups being equal also meant that the two drugs were given in a ratio almost equal to their predicted potencies of 200:1. We emphasize that these agents were administered intraoperatively and postoperatively according to objective criteria (see Methods section). Thus, in the clinical setting, an initial dose of 300 $\mu\text{g}/\text{kg}$ nalbuphine, followed by supplementary doses of 150 $\mu\text{g}/\text{kg}$ appears similar to fentanyl in terms of analgesic efficacy and duration. This is amplified by the observation that the patients' self-ratings of their overall postoperative analgesia showed no difference among groups.

We also found that the 500 $\mu\text{g}/\text{kg}$ loading dose of nalbuphine did not appear to confer any increase in duration of analgesia as judged by dosing frequencies. This may relate to the so-called ceiling effect described by Gal and co-workers (4). An initial intravenous dose of 150 $\mu\text{g}/\text{kg}$ nalbuphine in six male volunteers produced a 40% increase in pain tolerance but continued administration of the drug up to a cumulative dose of 600 $\mu\text{g}/\text{kg}$ over a 2-hr period produced no further increase in analgesic effect or respiratory depression. On the other hand, Gal et al. stated that "unpleasant, psychotomimetic effects, although not prominent, occurred," but the frequencies of these side effects were not quantitated as a function of dosage. Gal and associates also commented that "marked drowsiness and sedation resulted and may provide an advantageous clinical feature, since they were not associated with profound respiratory depression." Our observations, in the light of the findings of Gal et al., suggest that the μ -receptor mediated effects of nalbuphine, i.e., analgesia and respiratory depression, are overshadowed by κ -receptor effects, i.e., somnolence and sedation (5,6).

Our observation that three of the four patients who required overnight admission for excessive postop-

erative somnolence had received nalbuphine further suggests that this drug exerts greater κ -effects than does fentanyl, a predominant μ -agonist. In fact, these effects can be so striking as to make nalbuphine unsuitable in an outpatient setting. The incidence of nausea and the need for anti-emetic agents were also greater with nalbuphine, another disadvantage in an outpatient setting. The incidence of psychological side effects including dreaming of any type, unpleasant dreams, and postoperative anxiety, effects that may be σ -receptor mediated, were all greater with nalbuphine, perhaps a function of the induction dose. Figures 2 and 3, showing the incidences of dreaming and nausea, suggest such a dose-effect relation with nalbuphine. Despite unequivocal documentation of nalbuphine's greater propensity for psychological side effects, patient acceptance of nalbuphine was high and differed little from their acceptance of fentanyl.

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Application of a New Method for Measurement of Plasma Methadone Levels to the Use of Epidural Methadone for Relief of Postoperative Pain

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MAGORA F, CHRUBASIK J, DAMM D, SCHULTE-MÖNTING J, SHIR Y. Application of a new method for measurement of plasma methadone levels to the use of epidural methadone for relief of postoperative pain. *Anesth Analg* 1987;66:1308-11.

A method is described for measurement of plasma methadone concentrations using a gas chromatographic technique that is rapid and specific and enables the detection of concentrations of <1 ng/ml in plasma samples of only 1 ml. The method, when used to determine the plasma methadone levels in patients given continuous epidural infusions of methadone

plus on-demand supplementation for relief of postoperative pain, showed plasma methadone plateaus of around 10 ng/ml (starting at 15 min and lasting over 2 hr) and 20 ng/ml (starting at 3 hr and lasting over the period of treatment) ($P < 0.001$) after an initial 2-mg methadone epidural bolus and with continuous epidural methadone. Mean plasma methadone levels of around 10 ng/ml were associated with pain relief. Analgesia could be safely maintained for 24 hr.

Key Words: ANALGESICS—methadone. MEASUREMENT TECHNIQUES—methadone. PAIN—postoperative.

Methadone, a long-acting opiate, today is infrequently used in the management of acute (1) or chronic (2) pain. This may be partly because the pharmacokinetics of methadone are such that, with prolonged administration, cumulative plasma levels of methadone high enough to be associated with undesirable side effects (3,4) may occur. We therefore developed a new method for measurement of plasma methadone concentrations and applied it to a study of plasma methadone levels in patients using a previously described technique of epidural infusion of methadone plus supplemental bolus injections of epidural methadone for relief of postoperative pain (5).

Materials and Methods

Reagents

Levomethadone hydrochloride and the internal standard, normethadone hydrochloride, were obtained from Hoechst AG, Frankfurt. The n-pentane, isoamyl alcohol, and toluene used for extraction were analytical grade from Riedel de Haen AG, as was the buffer solution, pH 10.00 (sodium tetraborate/sodium hydroxide solution). The sulfuric acid and sodium hydroxide solutions were prepared from distilled water and reagent grade chemicals.

Extraction Procedure

One milliliter of plasma was placed in a glass-stoppered centrifuge tube. After the addition of 10 μ l internal standard solution (containing 50 ng normethadone hydrochloride), 1 ml buffer solution, pH 10, and 3 ml n-pentane containing 5% isoamyl alcohol, the mixture was shaken for 20 min with a rotary mixer (Breda Scientific) and then centrifuged at 4000 rev/min for 10 min. The organic layers were transferred to a conically tapered, ground-glass centrifuge tube containing 0.2 ml 0.1 M sulfuric acid and then agitated for 15 sec in a Vortex mixer. After centrifugation for

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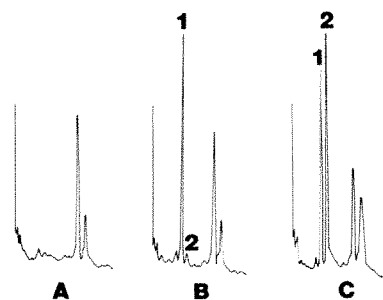


Figure 1. Chromatograms of (A) extract of a blank plasma and extracts of plasma samples spiked with (B) 1 and (C) 50 ng/ml methadone. 1, Internal standard; 2, methadone.

a short period, the supernatant organic phase was removed by vacuum. After alkalization with 20 μ l 5 M sodium hydroxide, the compounds were extracted with 20 μ l toluene by agitation for 10 sec in a Vortex. The aqueous phase was removed by syringing. Aliquots of 2 μ l were injected into the chromatograph.

Gas Chromatography

The gas chromatographic analyses were performed on a Hewlett-Packard model 5730A equipped with an NP detector and a Spectra Physics model SP 4270 integrator. The column was a DB1 Megabore fused silica capillary column with an internal diameter of 0.53 mm and a length of 30 m. The helium (carrier gas), air, and hydrogen flow rates were 30, 60, and 3 ml/min, respectively. The column oven was heated to 230°C, the injection port, to 300°C. The retention times were 1.63 min for the internal standard and 1.85 min for methadone. Figure 1 shows chromatograms of extracts containing methadone and a blank without internal standard.

Quantitation

Stock solutions (1 mg/ml) of methadone and internal standard were dissolved in methanol and kept cool. The stock solutions were diluted to an appropriate concentration with water to prepare standards by spiking blank plasma. About six standards within the concentration range from 1 to 50 ng/ml plasma were run with each batch of samples. Evaluation on the basis of peak heights was carried out using an integrator according to the international standard procedure. Day-to-day variation among identical standards is presented in Table 1. The extraction rate was about 70 to 80% for both compounds determined by comparing spiked samples with directly injected solutions of the compounds in toluene. The lower limit of detection was 0.5 ng/ml plasma.

Table 1. Day-to-Day Variation^a in Identical Plasma Samples ($n = 12$)

Concentration given (ng/ml)	Methadone (ng/ml)		Coefficient of variation (%)
	Mean	Standard deviation	
1.0	1.09	0.24	22.0
2.0	1.98	0.23	11.6
5.0	4.86	0.80	16.5
10.0	11.05	1.12	10.1
20.0	20.12	1.15	5.7
50.0	49.48	1.74	3.5

^aOver 6 days.

Postoperative Use of Epidural Methadone

With institutional approval and informed consent, eight patients (four men, four women; mean age, 55 $\pm$ 19 yr; age range, 28–81 yr) having undergone abdominal surgery under general anesthesia were included in the study. After induction of anesthesia, a catheter was inserted into the lumbar epidural space. Postoperatively, when patients reported severe pain, a bolus of 2 mg methadone was administered via the lumbar epidural catheter before initiation of a continuous infusion of 0.46 mg methadone per hour by means of an externally portable infusion device (5). During the first 2–3 hr, the pain score was recorded by one of the investigators. Thereafter, patients notified the nursing staff if pain developed. Subjective pain score was assessed using a visual pain analog scale (no pain = 0; severe pain = 5; intervals, 0.5). When pain exceeded 3, supplementary injections of 0.2 mg methadone were administered through the dosing device; in case of severe pain, a supplementary 2-mg bolus epidural methadone injection was given. The patients were supervised over the 24-hr period of treatment in the recovery room. Central venous blood samples (5 ml) were taken in heparinized tubes before and at various intervals (15, 30, 45, and 60 min and at 2, 3, 4, 5, 6, 8, 10, 12, and 24 hr) after the start of epidural administration of methadone for measurement of methadone concentration using the above-described method.

Data are presented as means $\pm$ SEM. Statistical significance was determined by using the programs BMDP 7D and P2V, Department of Biomathematics, UCLA, Los Angeles. Methadone consumption of the first and second 12 hr of treatment were compared with the paired *t*-test. Plasma methadone concentrations were compared by repeated measures analysis of variance and, in addition, by regression analysis. A value of $P < 0.05$ was considered to represent statistical significance.

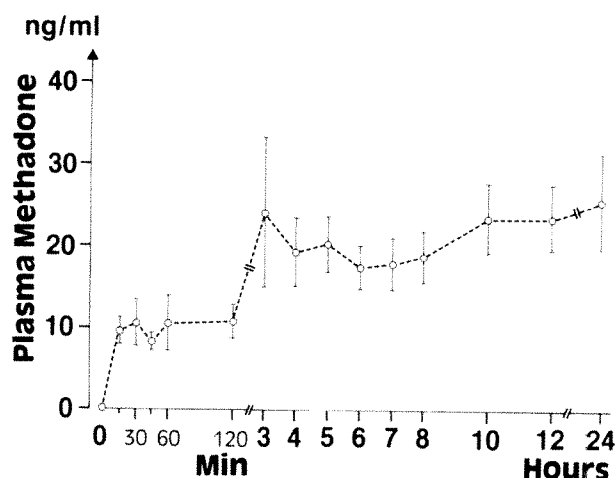


Figure 2. Plasma methadone levels associated with continuous epidural infusion of methadone plus on-demand epidural methadone for constant postoperative analgesia. Initial priming epidural injection of 2 mg methadone; constant basal infusion, 0.46 mg/hr; on-demand doses, 0.2 and 2 mg, when pain scores over 3 and 5, respectively (VAS no pain = 0, severe pain = 5; score intervals, 0.5) ($n = 8$, mean $\pm$ SEM).

Results

For constant analgesia during the 24-hr period of treatment, the patients required a total of 16.2 ± 0.8 mg methadone. In all patients methadone demand decreased significantly over the course of postoperative treatment. During the first 12 hr, 10.7 ± 0.8 mg methadone was required, whereas during the second 12 hr of treatment 5.5 ± 0 mg methadone sufficed for analgesia ($P < 0.05$). Plasma methadone concentrations showed two statistically significantly different plateaus of approximately 10 and 20 ng/ml, the former starting after 15 min and lasting over 2 hr, and the latter starting after 3 hr and lasting until the end of the period of observation (Fig. 2). Regression analysis showed a significant increase in plasma methadone levels with time. However, blood levels did not change significantly during the first 2 hr of treatment, nor did they change significantly between the third hour and the end of the study at 24 hr postoperatively, indicating that two separate plateaus of plasma concentrations were achieved.

Discussion

In comparison with other methods of measurement of methadone in biological fluids (1,6,7), the method described earlier is simpler and faster. The repeated use of 20 μ l toluol during the procedure also produces a two- to five-fold increase in sensitivity. A further increase in sensitivity is based on the long column employed, which is far longer than that used by others. Plasma methadone concentrations of 0.5 ng/ml

can be reliably detected using the described method, whereas the lowest detectable methadone concentration previously reported was 2.5 ng/ml (7).

The clinical results in the present study show a first plasma methadone plateau after the initial bolus epidural injection of 2 mg methadone and a second plateau that can be attributed to the continuous epidural methadone supply. The second plateau was associated with a decrease in the amount of epidural methadone needed to relieve pain. The plasma levels of methadone observed in the present study differ from serum morphine levels when epidural morphine is used in the same way to relieve pain (5). Serum morphine levels determined by a specific radioimmunoassay procedure increase rapidly after the initial bolus injection of epidural morphine before initiation of the continuous plus on-demand, epidural infusion of morphine for postoperative pain relief, during which they decrease (5). Depending on the amount of morphine administered epidurally each hour, a second peak serum concentration of morphine was found in intensive care patients requiring higher mean hourly amounts of morphine for analgesia in the early postoperative period than did nonintensive care patients (8).

The lipophilic, synthetic opioid methadone has a rapid distribution half-life of 15 to 35 hr (1,4,9-11); the minimum plasma methadone concentration associated with effective postoperative analgesia when intravenous injections are used averages about 31 ng/ml (15-50 ng/ml). Such concentrations were not always reached in our patients, but when they were, this did not occur until after 3 hr of treatment. Despite the delay in achieving peak plasma levels of methadone, the onset of pain relief occurred within 30 min after the beginning of treatment. This confirms the spinal site of action of epidurally administered methadone (12).

The persistence of plasma methadone within the range causing systemic analgesia in the course of the treatment explains why none of the patients required supplementary methadone during the second 12 hr of treatment. Moreover, during the whole period of treatment, plasma methadone remained in the non-toxic range. Thus, the epidural infusion of methadone plus on-demand epidural administrations, if necessary in case of insufficient analgesia, can be recommended as a safe and effective method for relief of postoperative pain.

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The Absorption and Degradation of Isoflurane and I-653 by Dry Soda Lime at Various Temperatures

Edmond I. Eger II, MD, and David P. Strum, MD

EGER EI II and STRUM DP. The absorption and degradation of isoflurane and I-653 by dry soda lime at various temperatures. *Anesth Analg* 1987;66:1312-5.

The capacity of dry soda lime to absorb and degrade isoflurane and a new inhaled anesthetic, I-653, was measured at normal, decreased, and increased temperatures. Both agents were absorbed at all temperatures tested (0, 20, 40, and 60°C). Absorption of isoflurane into a molecular sieve-like portion of dry soda lime was 30% (40°C) to 115% (0°C)

greater than that of I-653. Similarly, the quasipartition coefficient for dry soda lime was 18% (0°C) to 212% (20°C) greater with isoflurane than with I-653. Degradation rates for the two anesthetics were comparable, although slightly higher for I-653 than for isoflurane. Fractional degradation rates for both agents increased with increasing temperature and decreased as the concentration of agent increased.

Key Words: ANESTHETICS, VOLATILE—I-653, isoflurane. CARBON DIOXIDE, ABSORPTION—soda lime.

We have shown that all potent inhaled anesthetics in current use are degraded by dry soda lime (Strum, David P., unpublished data). Dry soda lime also absorbs much more anesthetic than does moist soda lime (1,2). Because drying of soda lime can occur in canisters that have a high flow of dry gases directed through them (e.g., the soda lime absorbers in an anesthetic circuit), we have further explored the degradation and absorption of isoflurane and a new, experimental anesthetic, I-653, by dry soda lime.

We chose these particular agents for several reasons. First, isoflurane is the most widely used, potent anesthetic in North America and is more stable than most potent inhaled agents (3). Second, the properties of I-653 suggest that it may displace isoflurane in some clinical areas. I-653 has a lower blood gas partition coefficient [isoflurane, 1.41 (4); I-653, 0.42 (5)] and this lower coefficient markedly accelerates recovery from anesthesia (6). The acceleration suggests that I-653 may be useful in anesthesia for outpatients. Third, I-653 and isoflurane are structurally identical except that I-653 has a fluorine rather than a chlorine atom on the alpha ether carbon. The substitution of fluorine

for chlorine increases resistance to degradation by moist soda lime, especially at temperatures above 60°C (7).

We asked whether I-653 was more stable than isoflurane at the higher degradation rates associated with dry soda lime and whether these two agents differed in their affinity for dry soda lime. We also tested whether the relative stability and affinity of these two agents was affected by the temperature of the soda lime.

Materials and Methods

We dried fresh soda lime (15 g H₂O/100 g soda lime) in sealed flasks to zero water content by simultaneously flowing 1–1.5 L/min of dry nitrogen gas through the flasks and heating the soda lime to 60–80°C. We also applied a vacuum of 0.3 atm to the exit ports on the stoppers. Drying time to a constant weight took about 3 days. The fresh soda lime was Sodasorb (W. R. Grace and Co.), 4-8 Tyler, 4-8 USS mesh, with an ethyl violet indicator.

We placed 85 g of the dry soda lime in 581-ml glass flasks. To prevent liquid (but not gaseous) anesthetic from reaching the soda lime, a Teflon cup was placed on top of the soda lime in each flask. A Teflon (rather than rubber) stopper was used to cap each flask so that anesthetic vapor would not be lost by dissolving in the stopper. Each stopper was pierced with a needle capped with a one-way stopcock to enable sampling. Each flask was evacuated to 0.3 atm to allow an aliquot of liquid anesthetic (Vi) to be drawn into the flask from a calibrated gas-tight syringe. Only one anes-

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thetic was delivered to a flask. From four to six different aliquots were used for each anesthetic at each temperature studied. The quantity of liquid isoflurane introduced ranged from 0.19–1.05 ml, and of liquid I-653 from 0.14–0.64 ml. Three flasks of each aliquot were studied at each of the following temperatures: 0, 20, 40, and 60°C. Flasks were maintained at these temperatures for 20 to 30 min before introduction of anesthetic and throughout the study.

One-half to 1 hr after injection of liquid anesthetic, the stopcock to each flask was opened briefly to permit the pressure in the flask to equilibrate with the ambient atmospheric pressure. Thirty milliliters of room air was then added to each flask and the flask resealed.

We monitored the decay of the vapor concentration for 20–30 hr after injection of anesthetic. Between three and five 10-ml samples of gas were drawn from each flask containing isoflurane, and the same number of 5-ml samples from each flask containing I-653. The smaller sample size was used with I-653 because these samples required dilution, thereby precluding the need for a larger sample. The sampling intervals were dictated by the rate at which anesthetic was degraded, e.g., degradation was more rapid at higher temperatures and thus required sampling at closer intervals. We repeated this protocol at 20°C with soda lime containing 6.2% moisture.

Anesthetics were analyzed by gas chromatography. We used a Gow Mac model 750 gas chromatograph equipped with a 30-m long, fused silica, open tubular capillary column (0.53 mm internal diameter) coated with a 5- μ m thick layer of methylsilicone oil (J & W Scientific DB-1). A nitrogen carrier stream of 6 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop. The chromatograph was calibrated with a secondary tank standard that had been calibrated with primary standards produced by injection of a liquid aliquot of anesthetic into a flask of known volume.

Data Analysis

The logarithm of the anesthetic concentration from each sample for each flask was regressed as a function of time. This permitted the calculation, by extrapolation, of the anesthetic concentration at time zero (C_0) for that flask.

Rates of anesthetic loss were expressed as a fractional decrease in the anesthetic vapor concentra-

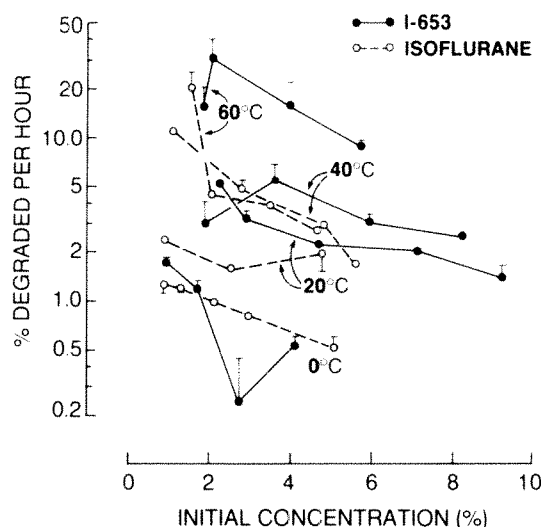


Figure 1. The degradation of isoflurane and I-653 by dry soda lime is inversely related to the initial concentration and directly related to the temperature at which exposure was carried out. At a designated temperature and concentration, the degradation rates for the two anesthetics are roughly comparable, being somewhat greater with I-653.

tion/hr (HL). The actual volume (ml) of anesthetic degraded in the first hour (DR) was calculated as:

$$DR = \frac{(V_i DI MV HL 10)}{MW}$$

where MV is the molecular volume of a gas at STP, DI is the density of the liquid anesthetic, and MW is the molecular weight of that anesthetic.

A second regression analysis was performed on the C_0 values as a function of the volume (ml) of liquid anesthetic added to the flask (V_i). Not all the C_0 values were used because a deviation from linearity (a "dogleg") was apparent for values below 1–2%. Thus we used the three highest triplicate sets of C_0 values, all >2%. The x-intercept of this second regression identified the capacity of the soda lime for anesthetic (V^*) at each specified temperature.

The quasipartition coefficient (Q) indicates the ratio of anesthetic partial pressure to anesthetic concentration in solution in the soda lime. Like any partition coefficient, the quasipartition coefficient is a unitless number. It was calculated according to the method of Grodin et al. (1):

$$Q = \frac{\left[\frac{DI MV}{MW} \right] - g \left[V_f - \left[\frac{S}{D_s} \right] \right]}{g \left[\frac{S}{D_s} \right]}$$

In this equation, g is the slope of the regression function when C_0 is plotted as a function of the volume

Table 1. Absorption Capacity (V^*) of 85 Grams of Dry Soda Lime

Temperature (°C)	V^* , I-653 (ml)	V^* , isoflurane (ml)
0	0.249 ± 0.023	0.536 ± 0.046
20	0.209 ± 0.018	0.382 ± 0.178
40	0.279 ± 0.028	0.364 ± 0.084
60	0.323 ± 0.066	0.476 ± 0.104

Data are presented as the average $\pm$ SD. $N = 9$ for all samples. Values at 0 and 60°C are significantly different ($P < 0.005$).

(ml) of liquid anesthetic added to the flask (V_i); V_f is the volume of the flask; S is the weight of soda lime added (85 g); and D_s is the density of the soda lime [e.g., 2.21 g/ml for dry soda lime (1)]. The quasipartition coefficient was calculated for each anesthetic at each temperature. The coefficient was corrected for the temperature at which it was determined. Student's t -test was applied and a Bonferroni correction made for comparisons.

Results

The rates of degradation of isoflurane and I-653 by dry soda lime were roughly equivalent at a given temperature and starting concentration (Fig. 1). There was no statistically significant difference in the rates of degradation of isoflurane and I-653, though there was a slight tendency for isoflurane to be more resistant. Degradation rates were inversely related to the starting concentration and directly related to temperature. Degradation rates were zero for isoflurane and I-653 in soda lime containing 6.2% water.

The absorption of isoflurane by dry soda lime was greater than that of I-653 (Table 1). Unlike degradation, the absorptive capacity did not change in a consistent manner with increasing temperature, tending to increase at both the higher and lower temperatures. The absorptive capacity of soda lime containing 6.2% water was low (0.037 ± 0.007 ml liquid I-653 and 0.078 ± 0.008 ml liquid isoflurane). The quasipartition coefficients for isoflurane were consistently greater than those for I-653 (Table 2).

Before exposure to dry soda lime, both isoflurane and I-653 gave a single chromatographic peak. As each anesthetic was degraded, a second, major peak appeared and continued to rise steadily with increasing duration of exposure. The source of this peak for both anesthetics was the compound, fluoroform. (Fluoroform was identified by gas chromatography combined with mass spectrometry [Vincent S. Venturella, PhD, personal communication].) Two minor peaks also appeared in the chromatograms for iso-

Table 2. Quasipartition Coefficients (Q)

Temperature (°C)	I-653		Isoflurane	
	g	Q	g	Q
0	11.8	28.3 ± 1.3	9.91	33.5 ± 1.7
20	21.6	9.84 ± 0.59	11.3	30.7 ± 7.4
40	23.0	11.0 ± 0.6	13.5	25.9 ± 3.1
60	18.5	19.0 ± 2.3	15.5	23.2 ± 3.5

The n per average value is 9; g is the concentration increase per ml of liquid anesthetic added to the 581-ml flasks. For the quasipartition coefficient, Q , the value for isoflurane was significantly greater than the values for I-653 at all temperatures (all P values were <0.005 except for P for the value at 60°C, which was 0.02).

flurane. No peaks other than those for I-653 and fluoroform were observed with I-653.

Discussion

Our results for the degradation of I-653 and isoflurane by dry soda lime (Fig. 1) confirm our previous findings at room temperature (David P. Strum, unpublished data). However, these data for dry soda lime are quantitatively different from those obtained in moist (fresh) soda lime containing 15% water (7). Degradation is far slower in moist soda lime and requires temperatures $>60^\circ\text{C}$ (7). Isoflurane is more resistant than I-653 to degradation in dry soda lime but less resistant in moist soda lime. We have no explanation for this difference.

The degradation of an anesthetic is of concern because of the potential for the development of toxic breakdown products. Such products have been found for halothane (8,9) and for older agents such as trichloroethylene (10). Fortunately, the breakdown product for both isoflurane and I-653 is fluoroform (trifluoromethane), an essentially harmless compound (11).

Our values for the absorption of isoflurane and I-653 by dry soda lime at room temperature (Table 1) confirm those obtained in earlier studies (David P. Strum, unpublished data). However, Grodin et al. (2) have reported significantly less absorption of isoflurane. Three explanations for this difference may apply. First, Grodin et al. (1) kiln-dried their soda lime at 120°C . We have found (unpublished data) that heating soda lime above 100°C decreases the absorptive capacity, as well as the capacity to degrade anesthetic. Second, we chose to exclude values obtained at low concentrations. If these lower values are used in the estimate of the intercept indicating absorption they will (falsely, we believe) lower that value. Third, Grodin et al. (2) used an infrared detector for their analysis of anesthetic concentrations. The infrared analyzer cannot distinguish the parent compound from

its degradation product(s). In addition, the fractional degradation of anesthetic is greater at lower concentrations (Fig. 1). Thus, the overestimate of agent by infrared analysis would be greater at lower concentrations. This would lower the intercept of the abscissa and thereby lead to a lower estimate of absorption. Our use of gas chromatography circumvented this problem. However, this third explanation is invalidated by the finding by Grodin et al. that no anesthetic was detected when the injected liquid volumes were below the absorptive capacity.

At all designated temperatures, the absorptive and solvent capacity of dry soda lime was greater for isoflurane (Tables 1 and 2). These factors indicate that dry soda lime will hinder the development of an anesthetizing concentration with isoflurane more so than with I-653. However, the higher concentrations of I-653 required for anesthesia would narrow this difference (12,13). A kilogram of dry soda lime continuously exposed to 1 MAC of isoflurane (1.38% [12]) at room temperature will take up 1300 ml of pure isoflurane vapor. Both absorption and solution are used to arrive at the figure of 1300 ml. Thus, the kilogram of dry soda lime will clear over 94 L of gas containing 1 MAC isoflurane. In contrast, a kilogram of dry soda lime exposed to 1 MAC of I-653 (5.72% [13]) will take up 1073 ml of vapor and will clear 19 L containing 1 MAC of I-653. We have used the MAC value for rats to calculate absorption and clearance/kg soda lime because data for MAC in humans are not available for I-653.

Consistent with the changes in solubility that usually accompany increases in temperature, the quasipartition coefficients for isoflurane decreased as temperature increased (Table 2). No trend was apparent in the data for I-653. We have no explanation for this latter finding.

Fortunately, soda lime infrequently becomes dry in clinical practice. The water content of soda lime can be sustained by the water vapor exhaled by the patient and by the water formed as carbon dioxide is converted to calcium carbonate by calcium hydroxide. However, water exhaled by the patient will not reach the soda lime, and conversion of carbon dioxide will

not occur if inflow rates equal or exceed minute ventilation. Low inflow rates increase the exposure of soda lime to exhaled water and carbon dioxide. Low inflow rates are likely to be indicated for I-653 because this new agent will be expensive. Although no figures are presently available, the raw materials required for its production (isoflurane and trifluorobromine) are costly. Moreover, the MAC value for humans is probably approximately 4% (13), further increasing the cost (relative to isoflurane).

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Clinical Reports

Reflex Sympathetic Dystrophy: A Complication of Interscalene Block

John H. Gillespie, DO, Emil J. Menk, MD, and Robert E. Middaugh, MD

Interscalene block of the brachial plexus is a reliable means for providing anesthesia of the shoulder and upper extremity. As with all anesthetic techniques, there are potential complications. The following case illustrates the occurrence of reflex sympathetic dystrophy (RSD) after an interscalene block with 3% 2-chloroprocaine. To the best of our knowledge, there is no previous case in the literature of RSD associated with interscalene block.

Case Report

The patient is a 70-yr-old man who was scheduled for removal of a foreign body in the right middle finger. Past medical and surgical history was unremarkable. The interscalene block was performed by inserting a 22-gauge needle into the interscalene groove (1). The brachial plexus was identified with a paresthesia radiating down the right extremity into the thumb. A total of 20 ml of 3% 2-chloroprocaine was injected incrementally. There was no pain or discomfort on injecting the anesthetic solution. The foreign body was removed in 15 min without difficulty.

The patient came to our pain clinic on the tenth postoperative day guarding and cradling his right arm with his left hand with a history of the development of a burning pain originating in the right shoulder and radiating into the right hand and thumb on the fourth postoperative day. The patient denied any previous injury or problem with his right extremity. Cold air increased the pain. Examination revealed an area of hyperesthesia over the distal brachial radialis mus-

cle tendon. Lightly touching hairs in this area of the hand caused excruciating pain. Skin temperature on the right arm was 36°C and 37°C on the left. A diagnostic right stellate ganglion block with 15 ml 0.25% bupivacaine was performed with immediate, total relief of pain. This was associated with the appearance of a right-sided Horner's syndrome and increased skin temperatures. There was no sensory or motor block. The patient returned to the clinic and received nine more sympathetic blocks over 10 weeks with increased duration of relief after each block. Physical therapy was used to exercise finger and wrist joints of the right hand after each block. The patient gained additional relief through the use of a transcutaneous nerve stimulator. At the conclusion of treatment the patient had 90% relief of his initial presenting symptoms.

Discussion

Reflex sympathetic dystrophy (RSD) may be defined as a disordered response by an extremity to trauma manifested by pain, vasomotor disturbances, delayed return of function, and trophic changes. None of these symptoms and findings may be related to the severity of trauma or injury to any specific tissue (2). Clinical features seen in RSD include pain (97%), swelling (69%), restriction of movement (88%), dystrophic skin changes (60%), and hyperesthesia (69%). The right upper extremity appears to be slightly more often involved than the left (3), the median and sciatic nerves being the most common peripheral nerves affected in RSD (4). Ischemic heart disease, cerebral vascular disease, cervical spondylosis, palmar fasciitis, and

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abdominal malignancies have been associated with RSD (5).

Many theories have been offered to explain the mechanism causing RSD. Livingston (6) postulates that the mechanism involves persistent afferent pain fiber stimulation with development of abnormal activity in the "internuncial pool" of the spinal cord that creates a large intracord burst of activity and subsequent continuous stimulation of sympathetic and motor efferent fibers. Melzak and Wall (7) in their gate theory proposed the location of specialized cells in the substantia gelatinosa of the dorsal horn that are capable of modulating afferent stimulation from sensory nerves. This information is carried by both small "C" fibers and large "A" fibers that are under constant cortical control. They suggest that large myelinated afferent fibers "close the gate," but impulses traveling along small "C" fibers "open the gate," thus allowing slight stimulation to be perceived as a great deal of pain. Doupe et al. (8) reported that partial nerve injury causes pathologic artificial synapses (ephase) between sympathetic efferent and sensory afferent fibers, thus creating cross-stimulation and direct summation. This may account for the marked burning pain and increased sympathetic stimulation of a distal extremity (9).

There is evidence that 2-chloroprocaine may reproduce neurotoxic injury to peripheral nerves. Barsa et al. (10) exposed intact rabbit vagus nerves to local anesthetic solutions and to physiologic salt solutions and demonstrated absent or marked impairment of conduction in nerves exposed to 3% 2-chloroprocaine. They also found histologic epineurial cellular infiltration and fibrosis, perineurial fibrosis, and axonal degeneration to nerves exposed to 3% 2-chloroprocaine, suggesting that this local anesthetic is more neurotoxic than are other local anesthetics (10). Myers et al. (11) also found that 3% 2-chloroprocaine, as well as 1% tetracaine, produce significant endoneurial edema 48 hr after treatment in intact sciatic nerves. They also showed that extrafascicular injections of clinically used concentrations are capable of altering perineurial permeability and thus producing changes in the environment of the endoneurium that result in neurotoxic injury. This study implicated the ester moiety rather than the vehicle, i.e., sodium bisulfite, as the cause of nerve injury (11).

Stellate ganglion blocks have been used in the diagnosis and treatment of upper extremity RSD. Bonica (12), for example, reported more than 80% success rate with stellate blocks in the management of RSD, whereas Wang et al. (13) reported a 74% improvement with repeat sympathetic stellate ganglion blocks, compared with 45% improvement in patients treated

with conservative therapy within 12 months of the onset of symptoms. Bonnelli et al. (14) found that intravenous guanethidine block provides even longer duration of block than do stellate ganglion blocks. Linson et al. (15) reported the treatment of upper extremity RSD with continuous stellate ganglion blocks.

We believe this is the first report of a case of RSD after interscalene block. We suggest the RSD was caused either by trauma from the 22-gauge B-bevel needle or from the 3% 2-chloroprocaine used. The improvement in the patient's condition with repeated stellate ganglion block demonstrates the importance of prompt as well as continuous therapeutic intervention.

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Brachial Plexus Anesthesia in Eight Patients with Recessive Dystrophic Epidermolysis Bullosa

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Recessive dystrophic epidermolysis bullosa (RDEB) is a rare (1;300,000) (1) chronic disorder of ectodermal structures. It is classified as a mechanobullous disorder (2), characterized by disintegration of the subepidermal connective tissue, with frictional separation of the epidermis by a split in the dermis, at a level below the dermoepidermal junction (3). This results in bullae formation after trauma, friction, or pressure. Originally described by Von Hebra (4), epidermolysis bullosa was further elucidated by Fox (5) and by Koebner (6) and more recently by Gedde-Dahl (3) and by Briggaman (7). The 16 forms of epidermolysis bullosa have since been categorized by genetic, clinical, and histologic criteria (3). RDEB is one form that is of special interest to anesthesiologists because of the involvement of mucous membranes. This presents a challenge to the anesthesiologist to maintain patency of the airway during an anesthetic without damaging epithelial surfaces. This problem has confronted anesthesiologists for decades; various techniques of general inhalation anesthesia have been proposed (8-14) with unsatisfactory results. As a result, ketamine (15-18) has emerged as a popular alternative to inhalational anesthesia for these patients, because its respiratory stimulation can minimize the need for instrumentation of the airway. The use of spinal, epidural, (19,20) and brachial plexus anesthesia (21) has been reported, but only in single patients. We present a series of eight patients given axillary block for repair of pseudosyndactyly secondary to RDEB.

Materials and Methods

Eight patients were operated on over a period of 8 months for pseudosyndactyly repair. These patients ranged in age from 5 to 8 yr and from 15 to 24 kg in body weight. They displayed typical stigmata of RDEB, including flexion contractures of the arms and legs, malnutrition, iron deficiency anemia, and multiple bullae. All had the classic "mitten type" pseudosyndactyly; none was receiving steroid therapy.

All patients were seen preoperatively and the anesthetic technique was explained as fully as the age of the patients would permit. The patients were not premedicated and they were transported via a Surgilift (Tomic Surgilift II Patient Handling System, American Hospital Supply, McGaw Park, IL) system to eliminate patient transfer between gurney and operating table. On arrival in the operating suite, intramuscular ketamine (5 mg/kg) was administered, resulting in loss of consciousness within 1-2 min. The following monitors were applied: a blood pressure cuff, gently wrapped over protective soaked gauze; a weighted precordial stethoscope; and three ECG pads, with the adhesive removed, carefully positioned under the patient's back. A tourniquet was fastened over protective gauze and an intravenous catheter was inserted percutaneously and wrapped in place with protective gauze; at no time was any adhesive tape used. The axillary site was soaked with an antiseptic solution and draped in a sterile fashion; no sponges were used for cleansing the skin. The axillary block was performed with a 2.75-cm 22-gauge needle, using the technique of axillary artery puncture based on injection of divided doses on both sides of the axillary artery; the musculocutaneous and thoracobrachial nerves were blocked with separate injections (22). Lidocaine 0.33 ml/kg of 0.5-1%, with 1:200,000 epinephrine was used as the anesthetic. Local anesthetic was not infiltrated subcutaneously. On successful completion of the axillary block, the patients were

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transferred to the operating room, where surgery commenced. An operating upper arm tourniquet was carefully placed over protective gauze and used for the hemostasis. Small supplemental doses of ketamine and/or diazepam were administered intravenously as needed for sedation during surgery. Operating time varied from 90 to 120 min.

Results

Operating conditions were satisfactory in all eight cases; only minimal amounts of intravenous ketamine (10–40 mg) or diazepam (2.5–5.0 mg) were needed for sedation. There were no complications from the axillary block, and meticulous handling of the patients resulted in formation of no new major bullae.

Discussion

Anesthesia in patients with recessive dystrophic epidermolysis bullosa requires a plan of management that minimizes contact with the skin or mucous membranes. Any well-administered anesthetic must begin at the bedside with a preoperative visit. Typically, these patients are malnourished and developmentally delayed; iron deficiency anemia, protein wasting, amyloidosis with associated impairment of renal function, and chronic steroid use are also common (21,23).

After review of the medical record and physical examination, the anesthetic technique should be carefully explained to the patient, in appropriate detail, to minimize apprehension. A calm patient in the operating room will prevent unnecessary agitation and thrashing that may result in the formation of new bullae. Many authors (12,17) recommend the omission of premedicants on the basis that an awake and alert patient can move himself and is likely to protect against the formation of new bullae.

We have found the Surgilift system to be particularly useful with these patients as it minimizes the trauma of patient transport to the operating suite. Once the patient has arrived in the operating room, the next decision that the anesthesiologist faces is appropriate intraoperative monitoring. Major bullae have been reported with the use of routine ECG pads (15); some authors have reported the safe use of needle electrodes (21,23). We modified the routine ECG pad by carefully trimming away all the adhesive and placing the remaining gel electrode under the patient. This provides an excellent ECG signal without causing formation of new bullae. Measurement of blood pressure with the Riva Rocca technique has been said to create shearing forces that can lead to the development of new bullae (17) and so many authors rec-

ommend that blood pressure not be measured in spite of the use of ketamine as the sole anesthetic; others have inserted a percutaneous catheter (24) into a peripheral artery to measure blood pressure directly. We found that carefully wrapping the arm with moist padding allowed the safe application and use of a blood pressure cuff without creation of new bullae. The use of a weighted precordial stethoscope provides a useful monitor of cardiac and respiratory function; total avoidance of adhesives will minimize associated skin trauma (8).

The major concern in these patients, as in all patients, is the maintenance of a patent airway. Mask fit can be a problem; merely applying the mask can generate the frictional forces adequate to create new bullae (19,25). If a face mask is necessary, generous application of lubricant and steroid cream to soft cotton wadding that is placed on the areas of facial contact (with both the mask and the fingers of the anesthesiologist) is in order (9,12). Once the mask is applied, care must be taken to ensure that movement of the mask is kept to a minimum to prevent damage to the skin. Insertion of an oral airway should be avoided, for massive bullae in the oral cavity may result (26).

At one time intubation of the trachea was avoided in RDEB patients, because it was felt that formation of laryngeal bullae could present an immediate threat to life following intubation. A search of the literature, however, has not revealed a single case of laryngeal bullae formation after use of an endotracheal tube. It is now felt that RDEB affects the stratified squamous epithelium of the oral cavity but not the pseudostratified ciliated columnar epithelium of the tracheobronchial tree (9). In spite of this, intubation may be fraught with difficulty. Scarring of the oral cavity, leading to microstomia, occurred in 51% of cases in the only major series of RDEB patients reported (25); 6% of these patients could not be intubated. If intubation is necessary, profound muscle relaxation is indicated, as movement during laryngoscopy may lead to the development of oropharyngeal bullae (13). Unfortunately, patients with RDEB often have large, dystrophic muscle masses that render them prone to a hyperkalemic response to depolarizing muscle relaxants (13,18). In spite of this, succinylcholine has been used uneventfully in these patients (11,12,24). If the patient is to be intubated, a well-lubricated MacIntosh blade is preferable to a Miller blade, to prevent trauma to the posterior epiglottis (14). Once intubated, the tube must be carefully immobilized to prevent movement in the oropharynx (12). Tape must not be used to hold the tube in place (8), and the tube must not exert lateral force at the corners of the mouth. At the time of extubation, it must be remembered that oro-

pharyngeal suctioning (27) can lead to life-threatening bullae formation. Finally, it should be noted that these patients have a high incidence of esophageal strictures increasing the risk of aspiration (18,19,21,24).

Ketamine has emerged as an attractive alternative for general anesthesia (15-18) as a means of avoiding many of the problems of airway manipulation during general anesthesia. Ketamine anesthesia, however, is not without side effects, including hypertension, tachycardia, and a violent emergence with thrashing and subsequent bullae formation (21). Despite these side effects, ketamine remains an important drug in the management of patients with RDEB.

As an alternative to general ketamine anesthesia, regional anesthesia has been recommended (10,12,19,20). A review of the literature, however, reveals that only single cases of the use of subarachnoid, epidural (19,20), and brachial plexus (21) anesthesia have been reported. Our series of eight patients who received brachial plexus anesthesia, allowing excellent operating conditions and minimal use of adjunct agents demonstrates, however, that peripheral nerve blocks are a safe, effective alternative to general, including ketamine, anesthesia in patients with RDEB. Previous fears of physical and chemical trauma to the skin with secondary bullae formation were not realized.

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Increased Incidence of Itching and Herpes Simplex in Patients Given Epidural Morphine After Cesarean Section

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Epidural morphine is commonly used for postoperative analgesia after cesarean section or gynecologic surgery (1). Its frequent side effects include pruritus, nausea, and vomiting; less frequently, ventilatory depression, urinary retention, or dysphoria occurs after epidural morphine (2-6). We have used this technique at our institution for several years and have noted it to be associated with an increased incidence of herpes simplex (HS) type I (labialis). To our knowledge, there are no published reports of HS after epidural morphine; HS after spinal morphine has been mentioned in one report (7). In the present study, we prospectively determined the incidence of HS and itching after epidural or intramuscular morphine in 44 women undergoing cesarean section.

Methods

At St. Elizabeth's Hospital, Turnhout, Belgium, 44 patients were studied with permission from the institutional review committee. Two groups were designated: group 1 comprised 26 patients who underwent cesarean section with an epidural anesthetic and were given epidural morphine postoperatively; group 2 comprised 18 similar patients who underwent the same procedure with an epidural anesthetic, but were given intramuscular morphine postoperatively.

All patients presenting for cesarean section were studied except those who received general anesthesia, by personal choice or as dictated by medical circumstances. Ninety percent of patients did, in fact, have epidural anesthesia. Epidural anesthetics were ad-

ministered by the attending anesthesiologist or a resident. Two epidurals failed, and general anesthesia was used; these two patients were excluded from the study.

Patients were informed before surgery of the choice of postoperative analgesia, that is, epidural or intramuscular injection of morphine. During the first, third, and fifth months of study, all patients received epidural morphine; in the second, fourth, and sixth months, patients received intramuscular morphine; the study lasted 6 months. No premedication was given. One patient in each group received antihypertensive drugs for preeclampsia. All patients had epidural anesthesia using 2% lidocaine with epinephrine 1:400,000; the average dose was 25 ml. Patients in group 1 received 5 mg morphine in 10 ml normal saline via the epidural catheter during surgical wound closure. The morphine was preservative-free, and a bacterial filter was used. An additional 3 to 5 mg of similar morphine in 10 ml normal saline was given epidurally up to twice a day for pain relief. The epidural catheter remained in place for an average of 2.3 days. Patients in group 2 were given 10 mg morphine IM up to several hours postoperatively and then up to 10 mg IM every 6 hr as needed for pain relief. The morphine given intramuscularly was the same as that used epidurally.

Patients were evaluated postoperatively for occurrence of itching and HS twice a day for 4 to 5 days and on the ninth postoperative day. All evaluations were either performed or confirmed by the investigator (Dr. Gieraerts). Itching was scored as mild, moderate, or severe on the basis of subjective patient discomfort. Dermatologic consultation was obtained to confirm the diagnosis of HS, and a biopsy was performed. The severity of HS was graded by degree (Table 1). In addition, previous history of HS was recorded. Itching was not treated; HS was treated topically with acyclovir.

Data were analyzed statistically using Fisher's exact

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Table 1. Classification of Herpes Simplex

Degree	Characteristics
First	One or two lesions <3 mm in diameter
Second	Three to six lesions <3 mm in diameter or one lesion >3 mm
Third	Large confluent lesions

test (two-tail) (8), with $P < 0.05$ considered statistically significant.

Results

Patients in both groups were similar in ASA physical status (1 and 2) and age (18–35 yr) (Table 2).

In group 1, 21 of 26 patients reported itching (Table 2). Itching was mild in 6 patients, moderate in 10, and severe in 5. Most frequently, itching started 2–5 hr after the first dose of epidural morphine. It occurred most commonly on the face, around the mouth and nose. One patient had itching after the first dose of morphine but not after the second. Ten to 14 hours after the last dose of morphine, itching had disappeared in all patients. In group 2, none of the 18 patients reported itching.

Herpes Simplex type I occurred postoperatively (from day 2 to day 5) in 9 of 26 patients in group 1 (Table 2). In an additional patient HS was present before cesarean section; no new lesions appeared postoperatively. Of the nine patients, two had first-degree HS, five had second-degree, and two patients had third-degree HS. One patient without HS showed diffuse facial erythema after the first dose of epidural morphine. No further epidural morphine was given to this patient. HS did not occur in any patient in group 2.

Eight patients in group 1 had a positive history of HS (Table 3). Three patients were eliminated from this subgroup: one had generalized facial erythema after the first dose of morphine, another had perioral herpes before surgery with no change after epidural morphine, and a third had had HS 1 week before cesarean section but had no recurrence after epidural morphine. Of the five patients remaining in the subgroup, four had postoperative HS. The other 18 patients in group 1 had a negative history of HS; HS occurred postoperatively in 5 of these. In group 2, although 3 patients had a positive history, HS occurred postoperatively in none of the 18 patients.

In group 1, we examined the relation between itching and postoperative HS (Table 4). Five of the eight patients with a positive history of HS had itching after epidural morphine. Of the 18 patients with a negative

history of HS, HS occurred postoperatively in 5, and all of these patients had itching. Of the 13 of 18 patients who did not show HS, 4 did not have itching and 9 did.

Discussion

We found a statistically higher incidence of itching in patients given epidural morphine for analgesia after cesarean section compared with patients given morphine intramuscularly. Also, we found a higher incidence of itching in patients receiving epidural morphine than has been reported in other studies (2,5,6). In our group 1, 21 of 26 patients (81%) had itching, most often around the nose and mouth (2). Itching sometimes occurred on the whole face, extremities, or thorax. In most cases, itching occurred 2 to 5 hr after the first dose of epidural morphine. It was not likely due to histamine release, because histamine release would be expected to occur immediately after administration of morphine (2). In all patients except one, itching recurred after subsequent doses of morphine.

We found a statistically higher incidence of HS in group 1 compared with group 2. The occurrence of HS after epidural morphine is largely undocumented. Crone et al. have conducted a prospective study (unpublished data), in which HS occurred in 20 of 556 cases of cesarean section; 18 of these 20 patients had received morphine epidurally. The incidence of HS in our study was higher than reported by these investigators and others (7).

In our study, the epidural administration of morphine may have been a triggering factor for the development of HS in women who underwent cesarean section. The herpes lesions were noted between days 2 and 5 postoperatively, and the lesions were in the perioral and perinasal regions, occasionally over the whole face. Recurrent disease seems to occur at the same site as the primary infection or in the same sensory innervation area (9). The centripetal migration of the virus from the site of infection along the sensory nerves to the ganglia has been recognized (9). Its later, centrifugal movement, by axonal flow to the peripheral nerves and epithelial cells, explains recurrent infection. Studies of latency in humans include the isolation of the HS virus from human trigeminal ganglia (9). This may explain why HS occurred on the face in our patients.

In group 1, parturients who had a previous history of HS tended to have a higher incidence of HS after epidural morphine, but this was not statistically significant ($P = 0.056$). Patients receiving intramuscular

Table 2. Incidence and Degree of Itching and Herpes Simplex After Intramuscular or Epidural Morphine

Group	Route of morphine administration	N	Age (yr)	Incidence of itching	Degree of itching	Incidence of herpes simplex	Degree of herpes simplex
1	Epidural	26	26.7 ± 3.8	21/26 ^a	1° 6/21 2° 10/21 3° 5/21	9/26 ^b	1° 2/9 2° 5/9 3° 2/9
2	Intramuscular	18	27.0 ± 2.6	0/18	—	0/18	—

Ages are means ± SD. ^a*P* = 0.001 by Fisher's exact test (two-tail).

^b*P* = 0.006 by Fisher's exact test (two-tail).

Table 3. Relation Between History of Herpes and Occurrence of Herpes in Patients Given Epidural (Group 1) or Intramuscular (Group 2) Morphine

Group	N	Postoperative herpes	No postoperative herpes
Group 1			
Positive history	5	4 ^a	1
Negative history	18	5	13
Total	23	9	14
Group 2			
Positive history	3	0	3
Negative history	15	0	15
Total	18	0	18

^a*P* = 0.056 by Fisher's exact test (two-tail).

morphine (group 2) with a positive history of HS did not have a recurrence of the disease.

The etiology of HS after the epidural administration of morphine remains unclear. Recurrence of HS infection is related to the type of HS virus, the immunologic status of the host, and the presence of a triggering factor (7,9). Most cases of HS in our study occurred around the nose and mouth, so we may presume that the viral agents were latent in the neuronal pathway of the trigeminal nerve, most probably in the gasserian ganglion (9).

With the use of epidural morphine, by contrast with intramuscular morphine, a higher concentration of opiates is found at the opiate receptors at the level of the substantia gelatinosa of the trigeminal nerve (2). The peak plasma level of narcotics after epidural administration, however, is similar to that of narcotics given intramuscularly. This similarity implies that the higher level of narcotics seen by brain stem opiate receptors is due to rostral spread of epidural morphine by way of the cerebrospinal fluid. Direct binding to opiate receptors in the medulla oblongata may be the mechanism for the occurrence of itching, related to altered sensory modulation (2,10). It may be that the HS viruses are reactivated by binding of morphine to these receptors. We think it more likely, however, that the viruses are reactivated indirectly by mechanical irritation of the sensory nerves in the

Table 4. Relation Between Itching and Herpes Simplex in Patients Given Epidural Morphine

	N	Itching	No itching
Herpes	9	9	0
No herpes	14	10	4
Total	23	19	4

face when patients scratch or rub the face in response to itching (9). All patients with postoperative HS indeed had itching as well.

Another explanation for the high incidence of HS after itching in our study might be altered immunologic response during the perinatal period or an increased level of beta-endorphins, which is known to occur during pregnancy. Other authors have stated, however, that itching does not follow intrathecal administration of beta-endorphins (2).

HS after delivery is of concern because the virus can spread to the infant and cause herpesencephalitis (11). Thus, in view of our findings, we recommend more caution in choosing epidural administration of morphine and giving subsequent doses for postoperative analgesia after cesarean section, especially in patients with a positive history of HS, until further investigations clarify the cause-effect relation.

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Vaginal Delivery Impeded by a Large Fetal Sacrococcygeal Teratoma: Anesthetic Considerations

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A large sacrococcygeal teratoma of a fetus can unexpectedly impede vaginal delivery after the fetus has been delivered up to the umbilicus. This rare occurrence—less than 1 in 400,000 births (1)—is associated with high fetal mortality and poor maternal outcome. Recently, obstetricians have attempted retrograde extraction of an infant via cesarean section (1). The only recommendation for anesthesiologists in such cases has been intubation of the fetus before the retrograde extraction (2). The present case report details the anesthetic problems and techniques for completing delivery of a fetus under these conditions.

Case Report

A 26-yr-old, gravida 2, para 1, woman at term and in active labor was admitted to an outlying hospital. Ultrasound at 8 weeks of pregnancy suggested a twin gestation, but this was not confirmed by other studies. Uterine fundus was noted to be unusually elevated at 35 weeks; ultrasound at that time demonstrated a normal fetus and a 12-cm mass. A uterine fibroid tumor or a degenerated second fetus were considered to be the cause of the mass. The pregnancy was otherwise unremarkable, as was the patient's medical and obstetric history, a previous pregnancy having been uncomplicated.

Cervical dilation and descent of the fetus occurred rapidly and was followed by spontaneous delivery of the head, arms, thorax, and abdomen to the umbilicus but further delivery was prevented by a large fetal sacral mass. The baby breathed spontaneously and

ventilation appeared to be adequate. While the baby breathed 100% O₂ through a loosely fitting mask, capillary blood gas values were pH 7.25; PCO₂, 48 mm Hg; PO₂, 83 mm Hg; and base excess, -6.5 mEq/L. An intravenous infusion of 10% dextrose in water was started in the hand of the child.

Arrangements were made to transport the mother and infant to a tertiary care medical center by fixed-wing aircraft. However, attempting to position the mother in the airplane before transportation compressed the baby and caused it to become cyanotic; therefore transportation was by ambulance. Approximately 8 hr after labor was impeded, the mother was admitted to our medical center and taken directly to the operating room. A plan of treatment had been discussed in advance among obstetricians, anesthesiologists, pediatric surgeons, and neonatologists and decided on; a pediatric anesthesia team and an obstetric anesthesia team had prepared for retrograde delivery via cesarean section. An adjacent operating room had been prepared for the possibility of an emergency surgical procedure on the newborn.

On arrival at the operating room, monitors were attached to the mother and the presenting parts of the infant, who was noted to be breathing spontaneously but not crying and who appeared to be weak. An automatic oscillometric blood pressure monitor attached to the arm of the infant showed a systolic blood pressure of 80 mm Hg, the ECG showed a sinus tachycardia of 180 beats/min, and a pulse oximeter applied to the ear showed an O₂ saturation of 94%. The infant's head and trunk were turned to facilitate direct oral intubation with a 3.5-mm endotracheal tube. Mechanical ventilation was instituted (F_IO₂, 100%). Arterial blood sampled from the right radial artery had a pH of 7.38; PCO₂, 24 mm Hg; PO₂, 168 mm Hg; and base excess, -7.0 mEq/L; bicarbonate, 5 mEq, was given to correct the metabolic acidosis. Anesthesia was induced in the mother with thiopental (3 mg/kg) and succinylcholine (1 mg/kg) before tracheal

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intubation with cricoid pressure. Anesthesia was maintained with 50% O₂ and N₂O and 0.5% isoflurane. During anesthetic induction for the mother, the infant became limp and unresponsive to touch and systolic arterial pressure decreased by 10 mm Hg.

A standard cesarean section incision was performed and a large sacrococcygeal teratoma was confirmed. Debulking or aspiration of the tumor to facilitate vaginal delivery was not feasible without jeopardizing the condition of the infant. Retrograde extraction of the infant through the uterine incision was planned. The umbilical cord was found to be pulseless and therefore was tied. The intravenous catheter inserted in the infant was heparinized, disconnected, and covered with a transparent sterile dressing in anticipation of the retrograde extraction. The blood pressure cuff, ECG leads, and oximeter probe were removed from the infant. Retrograde extraction was performed by reversing the normal order in which the fetus presents during delivery: abdomen, thorax, arms, and shoulders were passed through the cervix and into the uterus. The infant was then extubated, rotated quickly, pulled through the birth canal into the uterus, and delivered (3); the time from extubation to delivery of the infant boy was 20 sec.

The infant was taken immediately to the previously prepared, adjacent operating room, where he was immediately intubated and ventilated with 100% O₂. Apgar scores were 6, 4, and 5 at 1, 5, and 10 min, respectively. Initial systolic blood pressure was 40 mm Hg. The intravenous line was reconnected and 75 ml of blood was infused. Umbilical arterial and venous catheters were placed. Initial arterial blood gas values were pH 7.25; PCO₂, 23 mm Hg; PO₂, 503 mm Hg; and base excess, -10.8 mEq/L. Hematocrit was 51%, glucose, 80 mg/dl; calcium, 8.5 mg/dl; sodium, 133 mg/dl; and potassium, 5.0 mg/dl. The infant weighed 4120 g. The 500-g sacral teratoma, excised from the infant on the second day of life, was not malignant.

The infant required prolonged hospitalization. Areas of pressure necrosis near the perineum and upper thigh, presumably caused by prolonged pressure against the maternal pelvis, healed slowly. The infant is currently being treated for dislocated hips but otherwise has had normal growth and development.

Discussion

Large fetal sacrococcygeal teratomas are often associated with death in utero or premature delivery and neonatal death (4). The fetus may suffer cardiac failure with nonimmune hydrops and placentomegaly secondary to large arteriovenous fistulas and high output failure. When the fetus presents up to the umbilicus

and further delivery is prevented by a fetal tumor or mass, the outcome in the past has usually been fatal for the infant; debulking of the mass, which is destructive, followed by completion of vaginal delivery is rarely successful (5). The new technique of retrograde delivery of the infant via cesarean section has been successful (1). The anesthetic challenges involve anticipating problems of possible interaction between maternal and fetal circulatory systems throughout the ordeal and optimizing the condition of the infant immediately before retrograde extraction.

To what extent the partially delivered fetus in our case depended on the placenta and the umbilical cord and his own (i.e., pulmonary) circulation for oxygenation, ventilation, and other functions was not clear. The cord was not initially visible and could not be assessed for blood flow. Evidence suggesting a fetal circulatory pattern with dependence on the placenta and umbilical cord was that the child apparently lost consciousness during anesthetic induction for the mother, which indicates that the anesthetic agents used for induction reached the fetus via the placenta and umbilical cord. The anesthesia team had anticipated placental drug transfer and considered spinal or epidural anesthesia as the technique of choice (6); however, the mother could not be positioned for regional anesthesia without compromising the fetus.

The level of the infant's arterial oxygenation suggests a neonatal circulatory pattern and dependence on neonatal pulmonary circulation. The PaO₂ of the half-delivered infant during mechanical ventilation with 100% O₂ was 168 mm Hg. At that time, the mother was awake and breathing 100% O₂. In a report of the effects of maternal hyperoxia during epidural anesthesia on oxygenation of the fetus (*n* = 45), mean maternal PO₂ was 423 mm Hg (F_IO₂, 1.0) which corresponded to a mean umbilical venous PO₂ of 47 mm Hg (7); no fetus had a PO₂ greater than 53 mm Hg. The capillary PO₂ of 83 mm Hg and the later PaO₂ of 168 mm Hg in our infant must in part have been due to pulmonary oxygenation. Indeed, pulmonary blood flow is to be expected because the infant had already breathed air into his lungs. This decreases pulmonary vascular resistance and, thus, increases pulmonary blood flow (8). Because we anticipated effective pulmonary blood flow, we considered tracheal intubation and mechanical ventilation with 100% O₂ necessary to optimize oxygenation and ventilation of the infant immediately before retrograde delivery.

All the data indicate that our infant was in the extremely unusual position of depending on both pulmonary and placental circulations before induction of and during anesthesia. However, the extent of effective circulation from mother to uterine artery to pla-

centa to umbilical cord in our patient appeared to be minor; several considerations give evidence of a minor role. Uterine blood flow markedly diminishes after delivery (9). This may be caused by hormones or by the emptying of the uterus, either of which could have decreased uterine blood flow in our patient. Also, the umbilical cord was likely compressed between the infant's pelvis and the birth canal for several hours, which would have decreased blood flow. Indeed, the umbilical cord was found to be pulseless in utero during cesarean section. It is likely that the rate of blood flow in the cord was enough for drugs administered to the mother to have affected the fetus but not for pulsations to have been palpable.

The discussion of this infant's circulation raises the question of what factors cause the human umbilical artery to constrict (10). Epinephrine, histamine, vasopressin, oxytocin, hypoxia, and abnormal temperature do not affect umbilical artery muscle tone. Oxygen concentrations that produce hyperoxia (PO_2 of 680 mm Hg) cause slight constriction of the umbilical artery, but lower concentrations have little effect (10). The most dramatic constriction of the umbilical artery occurs with umbilical artery stretching. Possibly such stretching occurred for several hours during partial delivery and further stretching was likely caused by manipulation during cesarean section; thus, stretching of the umbilical artery was probably the major factor that decreased umbilical artery blood flow in our patient.

Optimizing the condition of the infant immediately before retrograde extraction involved continuous monitoring of blood pressure, ECG, arterial saturation, and arterial blood gas values, which were used as the basis for administering fluids, bicarbonate, and mechanical ventilation. Our goal was to protect the infant as much as possible from hypoxia, hypercarbia, and blood loss before and during retrograde passage through the birth canal and uterus. The cornerstone of therapy was intubation and ventilation with 100% O_2 before the retrograde delivery. The infant was extubated immediately before extraction, because vaginal fluids could have entered the infant's trachea through the tracheal tube. After delivery, the infant was quickly reintubated to continue resuscitation.

Several recommendations can be made from this unusual case of vaginal delivery impeded by a large fetal sacrococcygeal teratoma. A team of obstetricians, a neonatologist, a pediatric surgeon, and two sets of anesthesiologists, one each for the mother and infant, should agree as well in advance as possible on a detailed plan of management. Before cesarean section and retrograde extraction, the condition of the half-delivered infant should be optimized by tracheal intubation and mechanical ventilation with supplemental O_2 , volume resuscitation based on fetal blood pressure, and acid-base correction based on arterial blood gas values. Finally, a second operating room and appropriate personnel should be prepared to continue resuscitation of the infant after it is delivered and to correct the defect surgically if necessary.

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Varied Uses of a Thiopental Infusion

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Intravenous infusion of thiopental to treat seizures refractory to more conventional medication has in the past been considered an accepted, if rare, form of therapy (1,2). Likewise, the use of thiopental, either by infusion or by intermittent injection, as an adjunct to inhalation anesthesia has been described (3,4). At present, however, there are few generally accepted indications for thiopental other than for induction of general anesthesia. We present three case reports describing unusual circumstances in which a thiopental infusion was used, demonstrating that there still exist indications for the use of thiopental other than for the induction of general anesthesia.

Case Reports

Patient 1

A 20-yr-old, 60-kg woman was admitted to the emergency room in the throes of tonic-clonic seizures. The presumptive cause was a massive aminophylline overdose in an attempted suicide. The patient's trachea was intubated without the necessity for anesthesia or muscle relaxants. Over the next 30 min, 1 g diphenylhydantoin, 30 mg diazepam, and 260 mg phenobarbital IV did not stop the convulsions. However, IV increments of thiopental totaling 750 mg terminated the seizures within 5 min. A thiopental infusion was started at a rate of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ that was discontinued after 3 hr. Approximately 1 hr later the patient again began to convulse. A bolus of 200 mg thiopental immediately stopped seizure activity, and the thiopental infusion was resumed. During this time peritoneal dialysis was instituted to remove aminophylline. The thiopental infusion was discontinued after approximately 12 hr and the patient gradually

regained consciousness over the next 12 hr. She suffered no neurologic or other impairment.

Patient 2

A 23-yr-old, 55-kg, 6-weeks-pregnant woman was admitted to the emergency room with a fractured mandible and maxilla following a motor vehicle accident. Physical examination and past medical history were unremarkable. However, the patient's father had died under general anesthesia, suspected of having suffered an episode of malignant hyperthermia. General anesthesia was planned for reduction of the patient's facial fractures. An anesthesia machine that had never been exposed to volatile anesthetic agents was used. Blood pressure, ECG, hemoglobin-oxygen saturation, end-tidal CO_2 tension, and temperature were monitored. The patient was sedated in the operating room with $150 \mu\text{g}$ fentanyl IV, after which anesthesia was induced with 250 mg thiopental. Pancuronium 4 mg IV, was then given for muscle relaxation. After intubation of the trachea, the patient was mechanically ventilated with 100% O_2 . An additional $350 \mu\text{g}$ fentanyl was given, and a thiopental infusion was begun at an initial rate of $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ and adjusted to maintain systolic blood pressure $<130 \text{ mm Hg}$. The infusion was discontinued at the end of the 90-min surgical procedure, during which time a total of 650 mg thiopental had been administered. Muscle relaxation was not reversed. The patient resumed spontaneous respiration and regained full consciousness within 20 min. She had no memory of intraoperative events and reported satisfaction with the anesthesia.

Patient 3

A 60-yr-old, 70-kg man underwent coronary artery bypass grafting. Anesthesia for the 7-hr procedure was induced with $1200 \mu\text{g}$ IV sufentanil, 4 mg midazolam, and 5 mg droperidol, followed by 9 mg vecuronium, and was maintained with intermittent inhalation of isoflurane up to 0.6%, supplemented with

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25 mg pancuronium for muscle relaxation. Within 5 hr of arrival in the intensive care unit the patient began to emerge from anesthesia. Neuromuscular transmission had not returned sufficiently to allow tracheal extubation. Morphine 100 mg and 40 mg chlordiazepoxide were insufficient to sedate the patient and his increasing blood pressure could not be adequately controlled by sodium nitroprusside $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and IV 4 mg propranolol. Because cardiac output remained high at 8 L/min and pulmonary artery pressures were normal, it was decided to sedate the patient with thiopental. Two divided boluses totaling 125 mg were administered and an infusion was begun at a rate of $2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. The rate of nitroprusside infusion was reduced to $1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The blood pressure then decreased to normal values, cardiac output decreased to 6 L/min, and pulmonary artery pressures stayed in the normal range. The patient remained somnolent but arousable throughout the night. The thiopental infusion was discontinued after 5 hr, and the trachea was extubated 3 h later.

Discussion

The use of thiopental for control of status epilepticus is well known. It has not previously been reported, however, in association with the treatment of seizures caused by aminophylline toxicity. Such seizures can be refractory to more usual anticonvulsant agents (5).

Thiopental infusion as a primary anesthetic technique, as used in our second patient, has been described by Crankshaw and collaborators (6). However, they also used *d*-tubocurarine, fentanyl, and nitrous oxide. Another method of anesthesia utilizes thiopental by infusion, morphine by epidural injection, and pancuronium IV without the use of nitrous oxide or other inhalation anesthetics (7). Ours is the first reported case in which a thiopental infusion was used in combination with intravenous injection of muscle relaxant and narcotic, but without the use of any inhalation anesthetics. The rationale for selecting this technique was that nitrous oxide administered in the first and second trimesters of pregnancy might be hazardous to the fetus (8,9). Certain epidemiologic studies purport to document an increased number of spontaneous abortions among individuals chronically exposed to nitrous oxide (10,11), and the inhibitory effect of this agent on the enzyme methionine synthetase (12,13) would make the avoidance of nitrous oxide in early pregnancy seem reasonable if not necessary. Similarly, malignant hyperthermia susceptibility, whether proven or, as in this case, merely suspected, contraindicates the use of volatile inhalation anesthetics.

Thiopental infusion for sedation, as in our third case, is also a well-known technique (14), although its use is rare in the setting of open heart surgery because of its known cardiac depressant effect. However, one recent study does document the use of a thiopental infusion to provide neuropsychiatric protection in association with cardiopulmonary bypass (15), and it is known that the cardiac depressant effect of thiopental is dose related and is especially evident with rapid bolus injections (16). Our case report suggests that when ventricular function and cardiac output are satisfactory, a thiopental infusion may be a useful option for the purposes of sedation and blood pressure control in a hyperdynamic state.

In summary, we present three patients with clinical conditions in which thiopental administration by intravenous infusion proved to be useful, suggesting that there exists a wider role for this method than is at present generally assumed.

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Experience with Epidural Hydromorphone for Post-Thoracotomy Pain Relief

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Narcotics administered via the lumbar epidural route are useful in providing pain relief and preserving pulmonary function in patients who have undergone thoracotomies (1-3).

Hydromorphone (Dilaudid), a hydrogenated ketone derivative of morphine, has been given epidurally for postoperative analgesia (2), but no large series of cases has been reported using this drug for relief of post-thoracotomy pain. A possible advantage of hydromorphone when administered by the epidural route is its segmental effect, similar to that seen with the epidural injection of local anesthetics (4). When compared to other agents, this segmental effect should result in fewer side effects.

Methods

The charts of 21 patients who underwent thoracotomies during 1983 and who received epidural hydromorphone were reviewed. In the operating room all patients had a lumbar epidural catheter placed in the L2-3 interspace before induction of general anesthesia. Correct placement of the epidural catheter was confirmed when a sensory block was achieved after 10-15 ml 1.5% lidocaine with 1:200,000 epinephrine was injected through the epidural catheter. Narcotics were not given as a premedication. Only 2 of the 21 patients received IV narcotics (100 μ g of fentanyl) on induction of general anesthesia. No other patients received any parenteral narcotic intraoperatively. General anesthesia consisted of isoflurane in 100% O₂. All patients were given either 1.25 mg hydromorphone in 10 ml normal saline or 1.5 mg hydromor-

phone in 15 ml normal saline, injected epidurally approximately 45 min before the completion of surgery. Subsequent doses of 1.25-2.0 mg hydromorphone in 15 ml of normal saline were given when necessary as long as patients remained in the intensive care unit (ICU). The duration of action of the initial dose of epidural hydromorphone and the amount of supplemental intravenous morphine required while in the ICU were recorded. Only intravenous morphine was given for postoperative pain relief after the removal of the epidural catheter in the ICU. Side effects associated with epidural narcotics (respiratory depression, pruritis, and nausea) were noted when they occurred. Because all patients had indwelling catheters, the incidence of urinary retention could not be determined. All data are reported as mean $\pm$ SD.

Results

The mean age of the patients was 58.5 yr (range 18-76). In the operating room five patients received 1.25 mg epidural hydromorphone, and 16 patients received 1.5 mg epidural hydromorphone. Second doses of epidural hydromorphone in the ICU varied from 1.25 to 2.0 mg. Seventeen patients were given a second dose of epidural hydromorphone while in the ICU. The mean duration of the analgesia after the initial dose of hydromorphone was 7.7 ± 0.9 hr (range 3-18 hr). The mean ICU stay was 32.5 hr (range 19-70 hr). The total amount of intravenous morphine required while the patient was in the ICU averaged 4.4 ± 1.7 mg, an amount that includes that given to supplement the epidural hydromorphone as well as that required for analgesia after the removal of the epidural catheter. Two patients receiving 1.25 mg epidural hydromorphone and five patients receiving 1.5 mg epidural hydromorphone required an average of 3.6 ± 1.6 mg IV morphine to supplement the initial dose of epidural hydromorphone. Twelve patients required intravenous morphine after the removal of their epi-

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dural catheter while in the ICU. Six patients did not require any intravenous morphine while in the ICU. Three patients (14.3%) had a $\text{PaCO}_2 > 55$ mm Hg and were treated with intravenous naloxone. Two of these patients had been given a second epidural dose of 2.0 mg hydromorphone before the increase in PaCO_2 . No patients in our series had a respiratory rate < 8 breaths/min. Only one patient (4.8%) complained of pruritus, which was localized to the area around the oxygen mask. Two patients (9.5%) had nausea and vomiting.

Discussion

Excellent relief of post-thoracotomy pain has been achieved when morphine has been administered intrathecally (5) or through epidural catheters placed in the lumbar (1,2) or thoracic space (3). Unfortunately, epidural morphine has numerous side effects, including pruritis, delayed onset of respiratory depression, and nausea and vomiting (6-8).

It has been postulated that the degree of histamine release after intravenous narcotic administration is proportional to the concentration of the drug at mast cell membranes and to the number of drug molecules available to displace histamine from binding sites in the mast cells. Theoretically, hydromorphone administered intravenously should cause less histamine release than intravenous morphine because less drug is needed to produce a clinical effect and fewer drug molecules are competing for histamine-binding sites (9). The incidence of pruritis with epidural morphine when administered postoperatively is significant, varying from 11 to 70% (7,8). In our patients who received epidural hydromorphone, there was a very low incidence (4.8%) of pruritis. This might be because hydromorphone releases less histamine than does morphine (10). However, histamine release might explain only the onset of pruritis that starts relatively soon after the administration of epidural morphine. Pruritis after the administration of epidural narcotics usually starts by 1 to 3 hr (6). This suggests that differences in histamine release with epidural morphine and hydromorphone are not the basis for the differences in the incidence of pruritis.

In our series the incidence of nausea and vomiting was also very low (9.5%). This compares to the report of an incidence of 17-35% of nausea and vomiting with epidural morphine (7,8). Hydromorphone is seven to ten times as potent as morphine (11,12) and is eight to ten times more lipid-soluble than morphine (13). Because morphine is less lipid-soluble, when administered epidurally, it may remain in the spinal fluid

for long periods before binding to the spinal cord. Unbound morphine may travel rostrally through the CSF and bind to the areas of the upper cervical cord and the medulla (6). Bromage has hypothesized that pruritis may be caused by the effect of morphine on the caudal trigeminal nucleus causing sensory modulation. Nausea and vomiting may also be caused by the narcotic reaching the vomiting center in the brain stem (6). Because hydromorphone is more lipid soluble, it may have a more segmental effect with less rostral spread than epidural morphine. Horan et al. (4) reported a case where the level of analgesia with epidural hydromorphone was altered by administering the same amount of the drug but varying the volume of solution. This suggests a segmental effect from epidural hydromorphone.

Three of our 21 patients developed alveolar hypoventilation ($\text{PCO}_2 > 55$ mm Hg). Because two of these three patients received a large dose of hydromorphone (2.0 mg), this complication may have been dose related. We now limit our dose to 1.5 mg hydromorphone. Although the incidence of respiratory depression appears to be dose related, we still keep our thoracotomy patients in an ICU for at least 8 hr after the last dose of epidural hydromorphone. This has not caused problems because thoracotomy patients require intensive care supervision, and frequent monitoring by the nursing staff allows for early treatment with naloxone should the need arise. We did not encounter any cases of late respiratory depression in our series. In one report in which 5 mg of epidural hydromorphone was given by accident, there was not any late respiratory depression (14). To date there have not been any reports of late respiratory depression after lumbar epidural hydromorphone. There has been one reported case of late respiratory depression in a patient receiving hydromorphone through a thoracic epidural after an adrenalectomy for pheochromocytoma (15).

Hydromorphone, available as a preservative-free preparation, is less expensive than commercially prepared preservative-free morphine. The use of hydromorphone administered epidurally is currently not included in the manufacturer's guidelines. The Food and Drug Administration (FDA) restricts drug use to those applications that have undergone adequate controlled trials. The FDA does not limit the use of drugs to those applications that appear in the manufacturers guidelines. The FDA would define epidural hydromorphone as an "unlabeled application", that is, appropriate when a drug is used in a special situation not included in the manufacturers official guidelines (16). There have been other reports of the use of epidural hydromorphone (2,4,14,15) and, therefore, we

believe that epidural hydromorphone can be used clinically and not just for investigational purposes.

The duration of action was 7.7 hr in our patients, which is shorter than the average of 11.4 hr reported in the only other series using epidural hydromorphone for relief of postoperative pain (2). A possible explanation for this difference is that the duration of 11.4 hr was reported in patients having upper abdominal surgery, not thoracotomies. In a large series of patients receiving epidural morphine, only 17% of thoracotomy patients were pain-free after 12 hr, whereas 47% of laparotomies were pain-free 12 hr after receiving epidural morphine (8).

In our clinical experience, 12.5–1.5 mg hydromorphone in 10–15 ml of preservative-free saline administered via a lumbar epidural catheter provided excellent post-thoracotomy pain relief with fewer side effects than have been reported after epidural morphine.

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Flapper Valve Malfunction in an Ohio Closed Scavenging System

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Malfunctions of various parts of the Ohio Modulus anesthesia machines have been reported. Malfunctioning of the vaporizer selector interlock valve from a variety of causes including an abnormally short bushing (1), a loose Allen's screw (2), and a user-induced malfunction of the valve (3), has been reported. In all these cases the metered gases passed directly into the room without reaching either the vaporizer or the rest of the anesthesia circuit. When a mass spectrometer is used, absence of metered gases and the presence of nitrogen in the circuit can be noted (3).

Walters (4) and Bookallil (5) have documented intraoperative awareness secondary to air entrainment into the anesthesia circuit. The dilution of the inspiratory oxygen with air introduces the potential for arterial hypoxemia.

Ripp and Chapin (6) described a case of bellows leak of an Ohio ventilator due to a loose connection between the bellows and the bellows base assembly. The Ohio anesthesia ventilator uses two separate gas circuits, the pneumatic driving gas and the patient-bellows breathing circuit. A leak in the bellows can convert the two separate gas systems into a single system. This is associated with the potential hazard of diluting the anesthesia gases, pulmonary barotrauma and impedance to exhalation (PEEP) if the pressure in the housing surrounding the bellows increases above atmospheric pressure.

In this report the malfunction of the flapper valve of the scavenger valve (No. 7 in Fig. 1) leading to a significant loss of anesthesia gases is described. An Ohio Modulus I anesthesia machine with a free standing Ohio fluidic model number 800 ventilator was used.

Report of Two Cases

Case 1

A 23-yr-old man, weighing 60 kg, presented with an unstable pelvic fracture and was scheduled for open reduction and internal fixation of the pelvis with the application of Hoffman apparatus.

General anesthesia was induced with fentanyl and thiopental intravenously and isoflurane in 70% nitrous oxide and oxygen. After orotracheal intubation, he was placed in the prone position and ventilated mechanically using an Ohio fluidic ventilator model number 800. The ventilator (Fig. 2) has a down-falling bellows that refills by gravity (i.e., goes up during inspiration). The fresh gas flow in the anesthesia circuit was 3.0 L/min, and the ventilator was set to deliver a tidal volume of 900 ml at a rate of 11 breaths/min. It was immediately noticed that the chest expansion was inadequate and breath sounds were equal but weak. A negative pressure during part of the exhalation phase of the ventilator cycle was noticed, which was corrected by increasing the fresh gas flow to 5 L/min. On manual ventilation, the chest expansion was adequate and breath sounds were equal and well heard. A gas leak not in the anesthesia machine but somewhere in the ventilator or the scavenger system was suspected but could not be pinpointed. The low-pressure alarm system on the anesthesia machine did not indicate a gas leak. The ventilator was reset to deliver a tidal volume of 1000 ml and a rate of 15 breaths/min. Ventilation was judged adequate by clinical parameters, end-tidal CO₂ level using mass spectrometry, and repeated blood gas analyses. The ventilator and the scavenger system were carefully and repeatedly checked by several anesthesia personnel during and after the case, but there was no apparent gas leak.

Case 2

On the next day, using the same anesthesia machine, a 45-yr-old, 60-kg woman, ASA class II, was anes-

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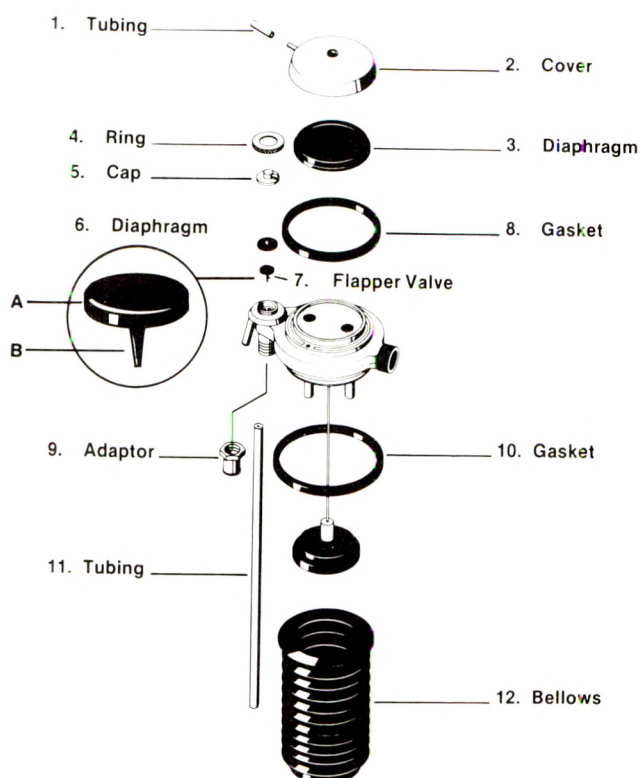


Figure 1. Parts of the exhaust valve of the scavenging system. The flapper valve (No. 7) of the exhaust valve is magnified in the circle. It is composed of a small rubber diaphragm (A) with a central stem (B).

thetized for lumbar spinal fusion in the prone position. General anesthesia was induced with thiopental, sufentanyl, isoflurane, and vecuronium. The trachea was intubated, and ventilation was controlled. The circuit fresh gas flow was 5.0 L/min, and the ventilator had to be set to deliver a tidal volume of 900 ml at a rate of 15 breaths/min. This large minute volume had to be used to achieve adequate ventilation, judged by clinical examination, end-tidal CO_2 levels, and repeated blood gas analyses. As in the previous case, repeated checking of the ventilator and scavenger system did not reveal any apparent leak. At the end of the case, the anesthesia technician was instructed to disassemble the ventilator and scavenger system and check all the parts. Using soap bubbles, he was able to find a damaged flapper valve of the exhaust valve (No. 7 in Fig. 1). When working properly, the flapper valve closes on inspiration and directs all of the gases toward the anesthesia circuit. On expiration it opens, directing all the gases toward the exhaust system. In these two cases, because the flapper valve was damaged, on inspiration it did not close completely and there was a gas leak. Most of the gases were shunted toward the exhaust system, which has less resistance

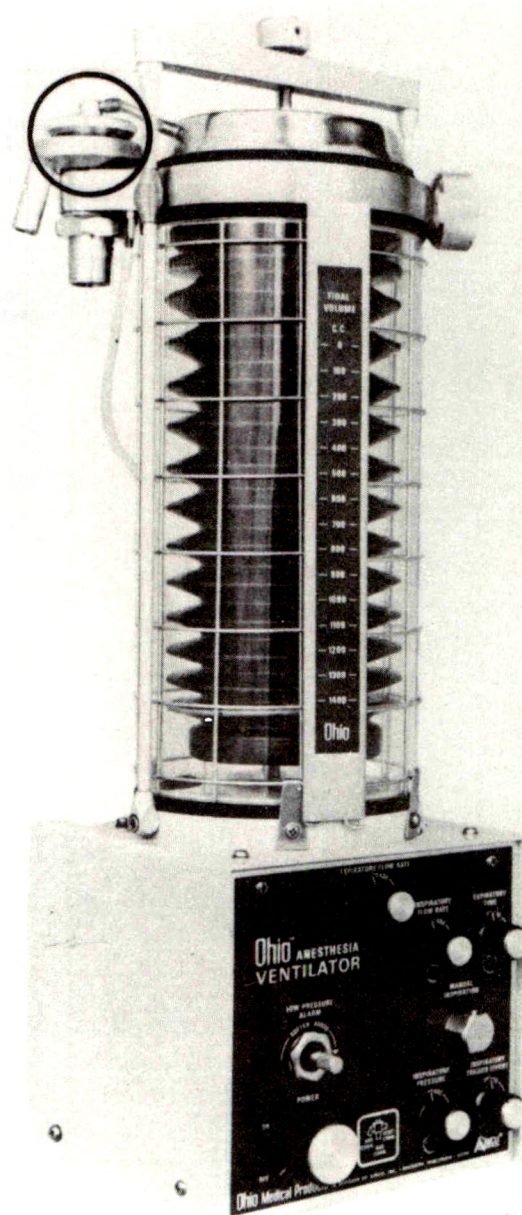


Figure 2. Ohio free standing ventilator model 800. It has a down-falling bellows that fills by gravity, i.e., it goes up during inspiration. The circle contains the exhaust valve of the scavenging system.

than the anesthesia circuit. Also, because the exhaust system is connected to suction, gases are directed to the scavenger system. This malfunction of the flapper valve of the exhaust valve occurred despite the fact that in our hospital there is a 3 month service on the exhaust system by the Ohio Company technicians. The low-pressure alarm in the anesthesia machine was not triggered because despite the gas leak, there was sufficient pressure in the system.

Discussion

The flapper valve of the exhaust valve of the scavenger system (No. 7 in Fig. 1) consists of a small rubber diaphragm (A) with a central stem (b). The stem has an indentation that holds it in place. On inspiration, when the flapper valve works properly, it fits tightly in its socket and prevents any gas leak to the exhaust system. On expiration, it opens and the excess gases pass to the exhaust system. In our two cases, the stem of the flapper valve (B) was defective, thus it did not seal off properly and the gas leak occurred. Accordingly, on inspiration, instead of having all the metered gases and the vapors directed toward the anesthesia circuit, part of the gases leaked into the scavenger system, which offers less resistance. The gas leak was not apparent because our scavenger system is a closed one. The gas leak was only diagnosed after disassembling the parts of the scavenger system and by using soap bubbles. The use of a closed scavenger system decreases the risk of operating room pollution and the potential harm to the operating room personnel (7).

Although large leaks in the anesthesia circuit should be detected by low-pressure ventilator alarms, this is not the case with the Ohio hanging bellows ventilator (8). The alarm is designed to trigger if a pressure of 10 cm H₂O has not been obtained for a period of 15 consecutive seconds. In our cases, despite the large leak, there was sufficient pressure in the anesthesia circuit that the alarm was not triggered.

Observing the anesthesia circuit pressure gauge can help to identify the source of the leak. A large gas leak may lead to a negative pressure during part of the exhalation phase of the ventilator cycle (9). In our first case, when the total fresh gas flow was 3 L/min, a negative pressure on exhalation was noticed for a short period. This was corrected by increasing the

total gas flow to 5 L/min. In the second case, a total fresh gas flow of 5 L/min was used from the start. The aim of this report is to alert the anesthesiologist to the possibility of a faulty flapper valve in the scavenger valve as a cause of loss of gases, which is not readily apparent when a closed scavenger system is used. This problem with the flapper valve is very difficult to pick up by a routine preoperative check of the machine. Normally, the ventilator and the exhaust system are not included in the circuit as part of check list and, in fact, it is almost impossible to design a preoperative check that would pick up this particular problem. Also, this report points out a disadvantage of this ventilator (Fig. 2) (the free standing Ohio No. 800 fluidic). The fact that the bellows refill by gravity permits the bellows to operate in a seemingly normal fashion despite the large gas leak.

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Letters to the Editor

Severe Bradycardia Following Epidural Anesthesia in a Patient With Idiopathic Hypertrophic Subaortic Stenosis

To the Editor:

Idiopathic hypertrophic subaortic stenosis (IHSS) is a hypertrophic cardiomyopathy characterized by asymmetrical septal hypertrophy associated with obstruction of the left ventricular outflow tract. The anesthetic management in patients with IHSS is directed toward minimizing the pressure gradient across the left ventricular outflow obstruction (1-3). The present report of a patient with IHSS who developed severe bradycardia associated with hypotension after epidural anesthesia shows that epidural anesthesia, similar to spinal anesthesia, may be poorly tolerated (2).

The patient was a 56-yr-old man who was diagnosed by echocardiography and cardiac catheterization as a case of IHSS. Echocardiography revealed asymmetrical septal hypertrophy, hyperdynamic contractility, and systolic anterior motion of the anterior leaflet of the mitral valve. Cardiac catheterization showed left ventricular end-diastolic pressure of 25 mm Hg, and a peak systolic pressure gradient of 100 mm Hg between the left ventricle and the aorta. The patient was managed by oral propranolol 120 mg three times a day and nadolol 80 mg twice a day.

The patient was scheduled for left inguinal herniorrhaphy under epidural anesthesia. The preoperative blood pressure was 100/60 mm Hg. ECG showed a normal sinus rhythm with a strain pattern at a rate of 50-60 beats/min with occasional ventricular premature beats. He was premedicated with oral diazepam 5 mg. On arrival in the operating room, he was hydrated with 1200 ml lactated Ringer's solution. Epidural anesthesia was then induced at L3-4 using 15 ml 2% lidocaine, which produced a T10 sensory level. After 30 minutes, the heart rate suddenly slowed down to 10-20 beats/min and the blood pressure decreased to 70/40 mm Hg. Atropine 0.6 mg IV increased the heart rate to 40 beats/min and a second dose of 0.6 mg increased it further to 80 beats/min and elevated the blood pressure to 110/65 mm Hg. The blood pressure and heart rate remained stable until the end of procedure; the patient's recovery was uneventful.

The predominant feature of the abnormal physiology in IHSS is decreased ventricular compliance with impedance to diastolic filling. Abnormalities of the systolic function result in a peak systolic pressure differential across the outflow tract of the left ventricle. The gradient is dynamic; it is aggravated by increased myocardial contractility or heart rate, and by decreased preload or afterload. On the other hand, the gradient is diminished by decreased myocardial contractility or heart rate, and by increased preload or afterload (1).

The abnormalities of diastolic function, as well as the systolic pressure gradient, can be aggravated by sympathetic stimulation and diminished by β -adrenergic blockade. Spinal or epidural anesthesia prevents the increased sympathetic stimulation associated with light levels of general anesthesia; it also induces preganglionic sympathetic blockade resulting in bradycardia and dilation not only of arteries and arterioles but also of the large veins and venules. Maximal venodilation usually occurs, resulting in venous pooling and decreased venous return to the heart (4). Thus, spinal or epidural anesthesia can produce two paradoxical effects in patients with IHSS: the decreased preload and afterload can aggravate the ventriculoaortic gradient, while slowing of the heart rate can improve the gradient. The net gradient is a balance between the two effects. In our patient, epidural anesthesia, despite fluid prehydration, resulted in serious bradycardia associated with hypotension. This might have been secondary to a critical decrease of venous return in the presence of IHSS, with a consequent increase of the left ventricular outflow obstruction. The bradycardia might have been exaggerated because of the β -adrenergic blockade therapy.

In conclusion, the present report shows that epidural anesthesia can induce severe bradycardia associated with hypotension in patients having IHSS. The response may be exaggerated in the presence of β -adrenergic blockade.

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Amantidine in Prevention of Fentanyl-Induced Muscle Rigidity

Muscle rigidity frequently is a major side effect of high-dose narcotic anesthesia. At this time, the mechanism remains undefined. There is evidence in animals that it is centrally mediated (1), and that dopaminergic neurons within the basal ganglia may be involved (2). Postulating this mechanism of action, we received approval from the human studies committee at the Massachusetts General Hospital to treat a patient preoperatively with amantidine-HCL, a drug that stimulates release of dopamine within the basal ganglia. The patient, a 60-yr-old, 60-kg woman, was given 100 mg amantidine-HCL orally every 12 hr for 5 days before scheduled surgery, for a total dose of 1 gram. She was also given 10 mg diazepam orally 1 hr before induction of anesthesia, after which she was given fentanyl 50 μ g/kg at a rate of 1 mg/min, a rate of injection that produces muscle rigidity in virtually all patients (3). After the fentanyl administration, she was anxious, but quite easy to ventilate. She developed no rigidity. She did however develop a slight tremor, remarkably similar to the "pill rolling tremor" of Parkinson's disease. She was then given 150 mg thiopental intravenously, after which she was quite flaccid and easily intubated without the aid of a muscle relaxant. The presence of a tremor and absence of rigidity suggests to us that the amantidine given was only partially effective in treating what we believe to be a Parkinson's-like rigidity caused by high-dose narcotics. We realize that this single case is inadequate to prove the mechanism of fentanyl-induced rigidity, but it may suggest a structural similarity between narcotic receptors and dopaminergic receptors in the basal ganglia involved in Parkinson's disease. This could have far-reaching implications. First, might various anti-Parkinson drugs given preoperatively prevent narcotic induced rigidity? Second, is it possible to treat Parkinson's disease with drugs that are structurally similar to narcotics, perhaps a narcotic antagonist? Also, one must consider whether patients receiving repeated high-dose narcotic anesthetics are at risk for developing Parkinson's disease in the future. Although there is certainly no evidence in the anesthesia literature to indicate this, there have been many reports of chronic abusers of "designer drugs" (fentanyl analogues) being stricken with Parkinson's disease.

We find this a very interesting problem, and though it may be some time before we can complete a formal study

on a large series of patients, we plan to continue our investigation in this area.

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Subclavian Venipuncture: A New Device Using a Doppler Probe

To the Editor:

Because the subclavian vein is situated behind the clavicle and is invisible even by echogram, access is difficult and subclavian veinipuncture may be associated with serious complications such as pneumothorax and hemothorax. We have developed and tested a new device that can detect vessels located behind bone. The system consists of a Doppler flow detector with three additional components: a transmission transducer that emits an ultrasonic wave (5 mHz), and a reception transducer to which a removable needle puncture unit is attached, the reception transducer receiving the waves reflected by the vein (Fig. 1). The puncture unit consists of a needle, a cannula, and an adaptor for the reception transducer. The needle is filled with saline using an injector connected to the needle. The transmission transducer, placed in the supraclavicular fossa emits ultrasonic waves toward the subclavian vein situated behind the clavicle. In the supine position, the needle is introduced beneath the clavicle as in the standard infraclavicular approach. The needle is then moved gently in the horizontal plane while the waves reflected from the vein are detected. When the needle is advanced and pointed toward the surface of the subclavian vein, flow in the vein is noted as an audio signal. The vein is punctured by advancing the needle to the site where the audio signal is at maximum and where venous blood is aspirated. The needle is then removed and a catheter is inserted through the remaining cannula.

This device has been used successfully and safely in more than 30 adult patients requiring subclavian venipuncture. The ability to locate the vein easily and clearly has offered major advantages of safety and reliability. It has also proved to be very useful educationally. Use of this device with other vessels such as the radial or femoral arteries and the internal

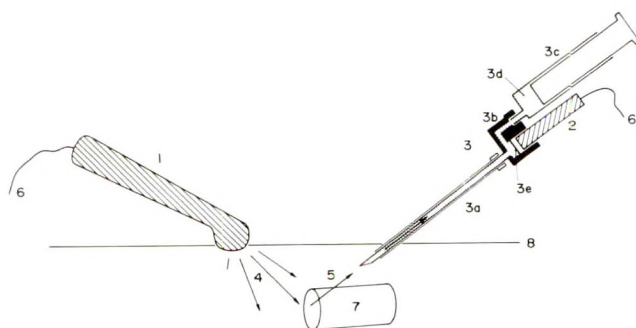


Figure 1. Access to the deep vein using an ultrasonic Doppler probe. Ultrasonic waves are emitted toward the vein. Venous flow is noted as an audio signal with the reception transducer. (1) transmission transducer with a handle; (2) reception transducer; (3) puncture unit; (3a) needle with a cannula; (3b) branch path; (3c) injector; (3d) normal saline; (3e) diaphragm; (4) ultrasonic wave: emitted; (5) ultrasonic wave: reflected; (6) connecting cords between transducers and main Doppler flow detector; (7) vein; (8) surface of the skin.

jugular vein may be equally helpful, though we have not yet examined this possibility.

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No Flow Anesthesia

To the Editor:

We wish to bring to your attention a potentially dangerous problem with the Ohmeda Modulus II anesthesia machine.

The fresh gas delivery hose (which connects the common gas outlet to the CO₂ absorber assembly) may be incorrectly routed by passing it over the assembly support arm, alongside the scavenger take-off port (Fig. 1A). When thus incorrectly routed, the gas delivery hose can become kinked and occluded when the assembly is rotated toward the front of the machine (Fig. 1B). Rotation of the assembly less than 20° can result in a sudden change from apparently normal fresh gas flow to complete obstruction.

We recently encountered this situation after an uneventful induction. We were halfway through the procedure when the absorber arm was rotated slightly to provide more room near the surgical field. The ventilator bellows ascended sluggishly, and attempts to fill the bellows and bag with the O₂ flush control valve were ineffective until the problem was identified and corrected.

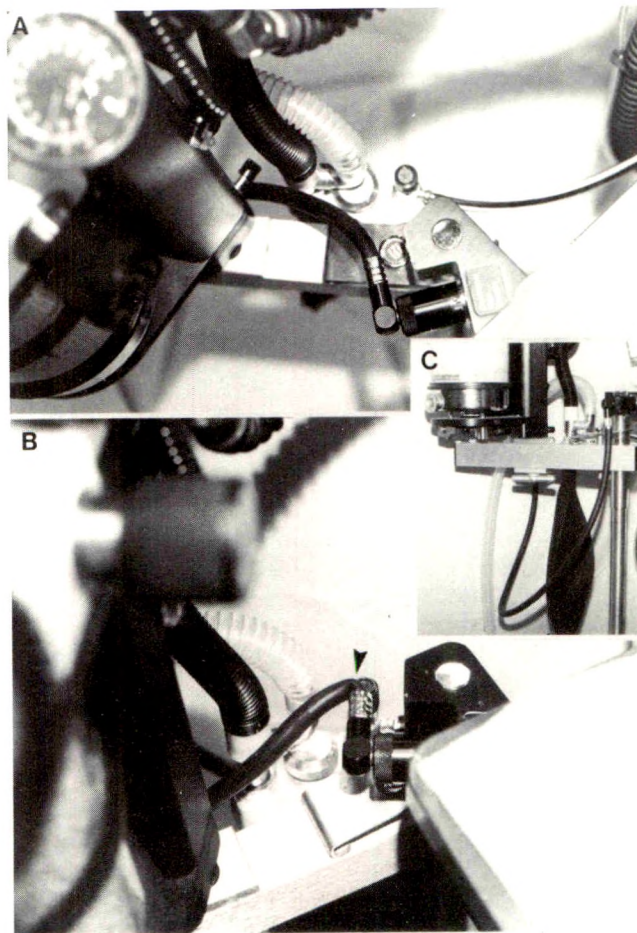


Figure 1. A) Incorrect routing of fresh gas supply hose over CO₂ absorber support arm; B) Occlusion (arrow) of hose by rotation of absorber assembly; C) Correct routing of fresh gas supply hose.

This problem can be avoided if the fresh gas delivery hose is correctly routed underneath the absorber assembly (Fig. 1C) instead of passing it between the canister and scavenger takeoff port.

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Are Local Anesthetics Equal?

To the Editor:

I read the interesting article by Dr. Phero and associates (1). They basically compared in humans isobaric tetracaine plus epinephrine, with bupivacaine alone. Their results showed no difference between the two groups in the incidence of spinal hypotension. They concluded that "the choice of local anesthetic agent, by itself, is not the sole cause of

hypotension seen with spinal anesthesia."

I have difficulty in agreeing with this conclusion. There are two pharmacologically active drugs in the first group, namely tetracaine and epinephrine compared to only one drug in the second group, namely bupivacaine. If tetracaine caused hypotension and epinephrine counteracted this effect while bupivacaine did not affect the blood pressure, the results in the two groups would have been similar. Therefore, using this study design, it is wrong to conclude that the hypotensive effect of the two local anesthetics is the same. To reach such a conclusion, either epinephrine would have been omitted from the study, or four groups would have been compared: in groups 1 and 3, either tetracaine or bupivacaine alone would have been used, and in groups 2 and 4, epinephrine would have been added to the specific local anesthetic.

It may be argued that the addition of epinephrine did not significantly alter the arterial blood pressure after spinal anesthesia (2). However, the quotation of a different study, especially from a different institution, is not valid since the circumstances are different.

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one of the five patients reported adequate analgesia (LAS < 5) but the analgesia, without cardiorespiratory changes, lasted only 75 min. Analgesia was inadequate (LAS > 5) in the other four patients and administration of conventional intramuscular analgesics was necessary within 30 min after epidural ketamine. These four patients also had hallucinations, reported blurred vision and felt uncomfortable. Two of them developed hypertension and tachycardia within 5 min after epidural ketamine.

In contrast to the previous reports (3,4) we did not find that epidural ketamine produced adequate analgesia after abdominal surgery. Although we only studied a small number of patients, epidural ketamine was unpredictable in its analgesic effect. Analgesia was too often insufficient and accompanied by undesirable side effects. We therefore believed it was no longer justified to continue the study. More information is needed about the absorption, pharmacokinetics and medullary effects of epidural ketamine before further clinical studies of epidural ketamine for relief of postoperative pain are undertaken.

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Epidural Ketamine for Postoperative Analgesia

To the Editor:

Recent publications indicate that ketamine, a phencyclidine derivative and potent analgesic, interacts as agonist with opiate receptors (1,2). Other publications (3,4) report the successful use of small doses of epidural ketamine for postoperative analgesia. Systemic side effects, motor block, and respiratory depression were not noted in these studies in which doses of 120 mg ketamine were given over 24 hours.

We recently conducted a pilot study to evaluate epidural ketamine as a postoperative analgesic.

Five patients ASA status I or II were given a single injection of 75 mg epidural ketamine when they reported severe pain after abdominal surgery. Heart rate, mean arterial pressure, respiratory rate, pain sensation evaluated with a linear analog scale (LAS), and sedation were measured before and at various intervals after injection. Only

One Cap Too Many

To the Editor:

We enclose two photographs (Figs. 1 and 2) of an elbow joint of the disposable tubing in current use at our hospital. The obstructing luer lock cap is one usually placed on the gas sampling port and was jammed tightly in the proximal end of the elbow. The obstruction was detectable neither by testing the circuit by inhalation by the anesthetist nor by obstructing the distal end and applying positive pressure to the reservoir bag. Also, the cap is not visible through the semi-opaque elbow.

This was discovered during administration of an anesthetic when there appeared to be incomplete airway obstruction in a patient breathing spontaneously via a mask. Endotracheal intubation did not relieve this obstruction. Having checked the endotracheal tube position, patency

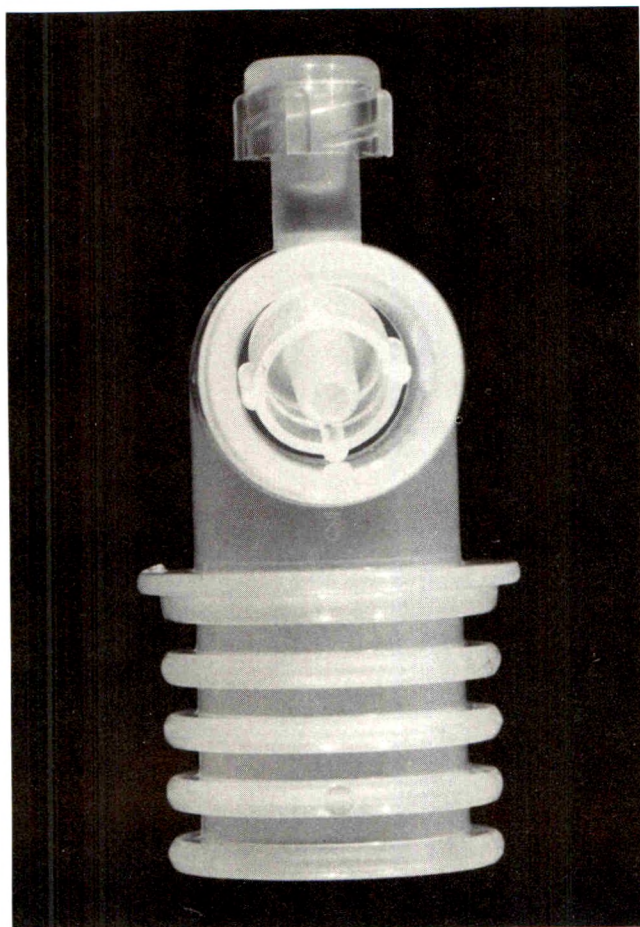


Figure 1

and cuff, we inspected the circuit and changed the elbow joint. The anesthetic then proceeded uneventfully, and the patient recovered with no ill effects.

The manufacturing company was contacted. As a result they have included in their final packaging a 100% visual inspection inside the elbows of all their disposable circuits.

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Preoxygenation Techniques

To the Editor:

We read with interest the comparison by Gambee et al. (1) of four vital capacity breaths with 3 minutes tidal breathing for the preoxygenation of general surgical patients. A significantly faster rate of arterial desaturation during apnea was found with the vital capacity technique. We have dem-



Figure 2

onstrated similar findings in pregnant patients.

We measured the end-expired oxygen concentration achieved after both four vital capacity breaths and 3 minutes tidal breathing in 20 patients at 38-41 weeks gestation. The end-expired oxygen concentration will correlate with alveolar values. Each patient performed both techniques in random order, thus acting as their own controls. Breath by breath expired oxygen concentration was measured with a Medishield MS2 quadrupole mass spectrometer sampling from a gas port in the anesthetic face mask. A circle breathing system was used with a 10 L/min fresh gas flow, and all patients were studied in the supine 15° left tilt position.

The end-expired oxygen concentration achieved with each technique is shown in Table 1. The aim of a preoxygenation technique is to optimally increase the volume of oxygen stored in the functional residual capacity (FRC) of the lung so as to delay the onset of arterial desaturation during apnea. The significantly lower ($P < 0.01$) end-expired oxygen concentration achieved by the vital capacity technique implies suboptimal preoxygenation.

Norris and Dewan (2) advocated the use of the four vital capacity breath technique for pregnant patients based on studies of P_{aO_2} achieved in two study groups. However, the wide inter-patient variation in alveolar arterial oxygen gradient seen at term pregnancy (3) makes comparison of techniques by this method difficult if patients are not used as their own controls.

Table 1. End-Expiratory Oxygen Concentration Achieved After Four Vital Capacity Breaths Compared with 3 Minutes Tidal Breathing

	FE ₀₂ achieved mean % (SD)
Tidal breathing 3 minutes	88.3(8)
Vital capacity breathing four breaths	78.3(4)

Pregnant patients have a reduced FRC and an increased basal oxygen requirement (4), and so are particularly prone to hypoxia. Preoxygenation must therefore be optimal. This study, and our work with a variety of other breathing circuits (5) strongly supports the results of Gambee et al. We therefore urge the use of at least 3 minutes tidal breathing for preoxygenation of all high risk groups.

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Does Diaphragmatic Paralysis Precede Hand Paralysis with Vecuronium?

To the Editor:

I read with interest the report by Chauvin et al. (1) on the effect of vecuronium 0.1 mg/kg on the human diaphragm. I was surprised by the conclusion that complete paralysis of the diaphragm occurred **before** that of the adductor pollicis. This is contrary to my own clinical experience using vecuronium at this dose for tracheal intubation. We have frequently noted that after induction with thiopental and complete paralysis of the adductor pollicis, as determined using peripheral nerve stimulation of the ulnar nerve, our patients will buck or cough on placement of an endotracheal tube. Furthermore, in thoracic cases, we have noted situ-

ations in which the adductor pollicis can be paralyzed using a bolus of vecuronium at a time when diaphragmatic movement still occurs.

Bencini and Newton (2), in a study of the rate of onset of good intubating conditions and hand muscle paralysis after vecuronium, 0.1-0.2 mg/kg, concluded that waiting 30 sec after 100% paralysis of the adductor pollicis resulted in better intubating conditions (including less bucking and coughing) than intubating the patients at 90-100% paralysis of the adductor. Similarly, Fahey et al. (3) have shown that conditions for tracheal intubation after complete paralysis of the adductor pollicis are not ideal, with coughing seen in some patients.

The clinical observations and the reports cited suggest that the phrenic nerve may not have been supramaximally stimulated in the study of Chauvin et al. (1) with the result that diaphragmatic paralysis appeared to precede that of the adductor pollicis.

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In Response:

We observed that the onset of abolition of the diaphragmatic mechanical response to single twitch phrenic nerve stimulation occurred before that of the adductor pollicis muscle after vecuronium (1). Despite its faster onset of paralysis, the human diaphragm is still resistant to muscle relaxants as shown by Donati et al. (2) with pancuronium. How can we explain this apparent contradiction and answer to Dr. Sosis's criticism? Onset of neuromuscular blocking effect is mainly influenced by the local muscle blood supply (3), which we suggested to be higher in the diaphragm than in peripheral muscles (1). Assuming that the dose of 0.1 mg/kg vecuronium exceeds the full paralyzing dose for the diaphragm, then the complete abolition of the elicited diaphragmatic response to single twitch stimulation will precede that of the thumb. However, the suppression of the diaphragmatic response to single twitch phrenic nerve stimulation does not necessarily suppress diaphragmatic movements elicited by noxious tracheal stimuli. In that situation the physiologic phrenic nerve impulses are tetanic instead of a single twitch stimulation. The abolition of diaphragmatic movements requires not only a deeper degree of neuromuscular blockade than the abolition of the response to single twitch stimulation, but also a sufficient level of anesthesia and analgesia to suppress or attenuate the transmis-

sion of noxious stimuli. This latter factor most probably explains the discrepancies between different studies that compare the intubating conditions after vecuronium to the depression of the adductor pollicis response to single twitch stimulation. Bencini and Newton (4) observed that thumb twitch depression preceded satisfactory intubating conditions after 0.1 mg/kg vecuronium in lightly anesthetized patients. Fehey et al. (5) observed that intubating conditions were not always ideal, but a dose of vecuronium of only 0.07 mg/kg was used. Using different protocols for induction of anesthesia but the same dose of 0.1 mg/kg vecuronium, several other authors, which are omitted by Dr. Sosis, observed that satisfactory intubation conditions were met before complete depression of thumb response to single twitch stimulation (6,7). Finally, the argument that the shorter diaphragmatic onset time could be explained by a phrenic nerve stimulation below the supramaximal level is surprising. First, we clearly specified that the intensity of bilateral phrenic nerve stimulation was set up 10–20% above the threshold level to obtain a maximal stable response (1). Second, how could a noneffective level of single twitch of stimulation influence the onset time of neuromuscular blocking effect?

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Ulnar Nerve Palsy of Unusual Etiology

To the Editor:

Recently, after undergoing appendectomy under general anesthesia of 55 minutes' duration, a previously healthy 47-year-old man was found to have a classical left-sided ulnar nerve palsy. Recapitulation of events revealed that one of

the cutaneous electrodes for electrical stimulation of the ulnar nerve (to assess neuromuscular blockade) had been placed over the ulnar nerve groove of the left medial humeral epicondyle. The arm had been placed on an armboard in 80° abduction with the forearm and upper arm pronated. This resulted in the weight of the arm pressing on the electrode and the attached hard plastic connector of the wire leading from the nerve stimulator. Pressure on the ulnar nerve must have caused the palsy.

This complication is completely avoidable by placing the arm and forearm on the armboard in the externally rotated position. Traditionally cutaneous electrodes for monitoring of the neuromuscular junction are placed at the wrist (1). Because the maximal current output of our nerve stimulator is 30 milliamperes and the patient was a large man, we were concerned that electrodes placed conventionally over the ulnar nerve would not provide supramaximal nerve stimulation (2). We therefore placed one electrode at the wrist and a second at the elbow in the expectation that at least one of the electrodes would provide supramaximal stimulation. The unfortunate complication could easily have been avoided by proper positioning of the arm and forearm.

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Report of a Problem with a New Spinal Needle

To the Editor:

A new 26-gauge spinal needle (Spinocan) manufactured by Burrton Medical has been introduced and is included as a part of their new spinal anesthesia tray. Previously, spinal trays from several manufacturers have been supplied with a Becton Dickinson & Co. (B-D) 26-gauge needle. Following the introduction of the new needle, a number of experienced anesthetists noted that CSF flow during lumbar puncture for spinal anesthesia was delayed or absent.

To investigate this problem, the resistance of the needle was measured using a pressure monitor infusion pump (IVAC 560). Using lactated Ringer's solution, pressure at flows of 50 and 100 ml/hr were measured in five needles of each type. From these measurements resistance was calculated ($\text{resistance} = \Delta \text{pressure} / \Delta \text{flow}$). The mean resist-

ance to flow, ($\pm$ SD), for the Spinocan 26-gauge was 2.70 ($\pm$ 0.07) torr hr/ml. This resistance was almost twice that of the B-D 26-gauge: 1.29 ($\pm$ 0.21) torr hr/ml.

The difference in resistance was confirmed by observing the flow from each needle at a constant pressure head of 10 cm water. Time to first drop from the hub of the 26-gauge B-D needle was 96 sec ($\pm$ 23); with the 26-gauge Spinocan, it was 203 sec ($\pm$ 18). Times between successive drops from the needle hubs were 33 ($\pm$ 8) sec (B-D) and 57 ($\pm$ 2) sec (Spinocan).

A previous study of larger 25-gauge needles from the same manufactures has been reported by Messahel et al. (1). Their investigation concluded that the flow characteristics of the 25-gauge Spinocan was superior to the 25-gauge B-D. On the basis of our clinical experience and laboratory experiments, this does not appear to be the case in the newer 26-gauge size. In many cases in our clinical experience, the absence of flow of CSF generated sufficient doubt of a successful dural puncture to necessitate a second lumbar puncture. In most cases, without repositioning the introducer, a 26-gauge B-D needle demonstrated adequate CSF flow. These findings have been brought to the attention of the manufacturer. We conclude that the performance of the new Burron 26-gauge needle is inferior to the B-D 26-gauge spinal needle and that the characteristics of this new needle can be deleterious to good clinical practice.

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dose (group 2) had severe ptosis and difficulty in swallowing. It is doubtful that both the laryngoscopist and the observer were really unaware of the group the patient was in, because these side effects are very unlikely to happen with saline. Furthermore, differences in the incidence of bucking (72% in group 1 vs 62% in group 2) and percentage of excellent conditions for intubation (56% in group 1 vs 75% in group 2) were not statistically significant. The power of this study with 39 patients was, however, extremely low. Thus, the chances for detection of a clinically important difference were very small. The fact that a statistically significant difference was not found does not necessarily prove that a difference does not exist (2,3).

Despite these comments, the study by Sosis et al. should be lauded as the first study of the priming principle that addresses the issue from the standpoint of the balance between the advantages for the anesthesiologist and the undesirable effects for the patient. However, we believe that further studies are needed before we draw the conclusion that priming is useless.

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Let Us Not Bury the Priming Principle Too Quickly

To the Editor:

We read with interest the article by Sosis et al. (1) on the use of priming doses of atracurium. The authors conclude that priming does not significantly improve intubating conditions, that it is "complex, time consuming. . ." This is a rather drastic conclusion, especially because there are points in their method that deserve attention. First of all, the authors state that the study was done in a double-blind manner. On the other hand, most patients receiving a priming

In Response:

We thank Trepanier et al. for their interest in our report on priming with atracurium (ATR) (1). They state that our conclusions about priming are "drastic". However, I feel that priming has received excessive praise. Schwarz et al. (2), for example, in discussing priming, state that "the divided-dose method of administration . . . compensates for the relatively slow onset (and) provides excellent conditions for tracheal intubation just as rapidly as SCH" (succinylcholine) (2). Our data (3) show that this statement is incorrect and that priming may be dangerous.

Trepanier et al. are correct in noting that many patients in our priming group had ptosis and difficulty swallowing shortly after receiving their priming dose. We also noted (1) that 38% had reductions in maximal inspiratory force

and 19% were unable to sustain 5-sec head lift. This suggests that if priming with ATR were used in a rapid sequence induction in a patient at risk for aspiration, priming might put the patient at risk. Musich and Walts (4) have reported just such an occurrence with a priming dose of vecuronium.

Our results show that priming resulted in satisfactory (good and excellent) intubating conditions in 90% of our patients. This compares to 88% of the patients in our control group. We feel that expanding the size of our study will not show a clinically significant improvement of intubating conditions with priming. Furthermore, the question of whether 60 $\mu\text{g/kg}$ ATR given before 300 $\mu\text{g/kg}$ ATR results in improved intubating conditions as compared to a single bolus of 360 $\mu\text{g/kg}$ ATR is moot because this priming dose causes an unsatisfactory frequency of serious side effects.

Is priming with a dose of ATR that is expected to produce fewer side effects efficacious? Ramsey et al. (5) evaluated priming with 50 $\mu\text{g/kg}$ ATR and concluded that it was not. These views have been confirmed by others (6).

We agree with Trepanier et al. (1) that further studies of priming are warranted. For clinical practice, however, we recommend that in those rare instances in which a rapid sequence induction is necessary and succinylcholine is absolutely contraindicated, that a single large bolus of vecuronium (0.25 mg/kg) be used instead of a priming technique (7).

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Local Analgesia by Perineural Morphine Injection

To the Editor:

Mays et al. (1) report that perineural injection of morphine produces long-lasting analgesia without anesthesia in pa-

tients with chronic pain. They conclude that the mechanism of morphine-induced analgesia at the peripheral neural sites is independent of a local anesthetic-like effect.

Hunter and Frank (2) and Frank and Sudha (3) have shown that opioids and opioid peptides depress the amplitude of compound action potentials in A(delta) and C fibers in vertebrate neurons, an effect blocked by small concentrations of naloxone. They postulate the existence of stereospecific opioid receptors located on the inner surface of the cell membranes of peripheral vertebrate axons. Opioids can also produce a nonstereospecific, local anesthetic-like inhibition of action potentials (4). These two different actions of morphine on the peripheral nerves become, however, apparent at different concentrations. Receptor specific action usually requires smaller concentration of morphine than does local anesthetic-like action.

Mays et al. used a single concentration of morphine in their study. It is possible that the analgesia was mediated by one or both mechanisms. A more complete concentration-effect (dose-response) study of opioid agonist and antagonist is necessary before determining the exact mechanism of analgesia.

We are in agreement with Mays et al. (1) on the peripheral site of action of morphine. In fact, several pharmacologic (5,6) and electrophysiologic studies (7) have attested to the receptor-dependent peripheral analgesic action of morphine. Morphine injected intraarterially near the inflamed knee joints of cats inhibits spontaneous electrical discharges in nociceptive afferent nerves in a dose-dependent manner, an action readily reversible by naloxone (7). However, we believe that the data of Mays et al. are insufficient to rule out a local anesthetic-like action of morphine.

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Pharmacokinetic Analysis of Succinylcholine-Cimetidine Interaction

To the Editor:

Kambam et al. report that preoperative cimetidine treatment increases the duration of action of succinylcholine without affecting its onset of action (1). The data from this study lend themselves to additional pharmacokinetic analysis that may be useful in delineating the mechanism(s) involved in the interaction.

If it is assumed that succinylcholine is eliminated by apparent first-order monoexponential kinetics and that its metabolite(s) are inactive, then the duration (t) and the rate of decline (R) of effect (paralysis) can be related using the following equations, as derived previously for succinylcholine (2):

$$t = (2.3/k_{10})(\log A_0 - \log A_{\min})$$

$$R = m(k_{10}/2.3)$$

$$t \times R = m(\log A_0 - \log A_{\min}),$$

where k_{10} is the apparent first-order rate constant for drug elimination from its site of action, $A_{\min}$ is the minimal effective dose, and m is the slope of the response-log dose (A_0) relation for the relaxant. Thus, four pharmacokinetic terms determine the duration and rate of decline of effect; three of these terms (m , A_0 , and $A_{\min}$) appear on the right side of the last equation, whereas k_{10} is implicit on the left-hand side but cancels out as such. Thus, patients given the same dose of succinylcholine with or without cimetidine but showing different durations of effect, the product of duration (t) and rate of decline (R) of effect will yield a constant value if the differences in the observed time course of effect are solely the result of differences in the elimination rate constant (k_{10}). If, however, the values of $t \times R$ differ between the patients, then it must be concluded that these patients differ with respect to m and/or $A_{\min}$ and/or k_{10} .

The results reported in the control (no cimetidine) and treated (preoperative cimetidine) groups of Kambam et al. (1) are summarized in Table 1. As stated by the authors, all patients given cimetidine showed a longer duration of action and a reduced rate of recovery from succinylcholine. However, the tR values for all (but one) patients in both groups were remarkably constant despite wide variations in duration and rate of decline. Thus cimetidine pretreatment changes the elimination rate (k_{10}) of succinylcholine rather than affecting its minimal effective dose ($A_{\min}$) or affecting the relation between its elicited effect and log dose (m). That $A_{\min}$ and m are not affected is also reflected in similar onset times. Cimetidine prolongs the effect of succinylcholine by delaying its elimination from the body presumably via its general inhibitory effect on drug metabolizing enzymes, because succinylcholine's effect is probably terminated by its hydrolysis by plasma cholinesterase. Studies are now needed to determine the time-course of cholin-

Table 1. Pharmacokinetic Analysis of Succinylcholine-Cimetidine Interaction

Patient no.	Control group			Cimetidine group		
	t ^a (min)	R ^b (%/min)	tR (%)	t ^a (min)	R ^b (%/min)	tR (%)
1	7.4	6.08	44.99	17.4	2.59	45.07
2	9.8	4.59	44.98	9.4	4.79	45.03
3	10.4	4.33	45.03	56.3	0.80	36.03
4	6.4	7.03	44.99	19.6	2.30	45.08
5	7.4	6.08	44.99	19.4	2.32	45.01
6	3.3	13.64	45.01	10.4	4.33	45.03
7	7.4	6.08	44.99	18.6	2.42	45.01
8	8.8	5.11	44.97	14.5	3.10	44.95
9	5.9	7.63	45.02	16.5	2.73	45.05
10	10.8	4.17	45.04	12.4	3.63	45.01
Mean	7.8	6.47	45.0	19.5	2.90	44.1
± SD	± 2.2	± 2.6	± 0.02	± 12.8	± 1.08	± 2.7

^aTime from 95% twitch depression to 50% twitch recovery.

^bRate of decline of effect from 95% twitch depression to 50% twitch recovery.

esterase inhibition by cimetidine and to see if any of the newer H₂ receptor antagonists are better for use with succinylcholine. Incidentally, Patient 3 in the cimetidine group who showed an unusually long duration of action (and a very slow rate of recovery) had a low tR value compared with other patients, illustrating that he/she differed from others with respect to m and/or $A_{\min}$ in addition to k_{10} .

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Pulse Oximeters, One Lung Disease and the Rotabed

To the Editor:

Pulse oximeters are rapidly becoming the standard of care in operating suites. They provide an effective means of noninvasively monitoring arterial oxygen saturation (SaO₂) without the need for repetitive measurements of arterial blood gas tensions (ABGs). Pulse oximeters are also now being used increasingly often in intensive care units where arterial oxygenation may change as abruptly as in the operating room.

In patients with significant lung disease requiring prolonged intubation, it has become standard practice at our institution to use a device known as the Rotabed. This bed allows continuous slow turning of an intubated patient from side to side as a unit, thereby preventing pooling of lung secretions and improving pulmonary toilet. Although these devices decrease pulmonary morbidity, we have noticed interesting changes in SaO_2 in patients with unilateral pulmonary dysfunction as the bed cycles from side to side. As the Rotabed turns so that the diseased lung becomes dependent, dramatic decreases in SaO_2 as measured with the pulse oximeter can occur. Correlations between SaO_2 derived from ABGs and those measured with pulse oximetry can be seen (Table 1).

Patient #1 was a 27-yr-old man with right pulmonary contusion and fractured ribs T-4 through T-7. The second patient was a 39 yr-old-man with reexpansion pulmonary edema on the left, secondary to reexpansion of a hemothorax. Patient #3 was a 22 yr-old-woman with right-sided aspiration pneumonia identified by chest X-ray. The fourth patient was a 23-yr-old man with right pulmonary contusion as determined by chest X-ray with small (10%) right-sided pneumothorax (chest tube in situ). Patient #5 was a 33-yr-old man with reperfusion pulmonary edema after pulmonary thromboendarterectomy of the right pulmonary artery; complete opacification of the right lung field noted on chest X-ray.

If a single ABG were obtained in these patients while tilted on the Rotabed with the diseased lung dependent, unwarranted increases in FI_{O_2} and/or PEEP may have been ordered because such SaO_2 and PaO_2 values would imply significant impairment of oxygenation. Continuous pulse oximetry allowed the cyclical nature of these desaturations

Table 1. SaO_2 as Determined by Pulse Oximetry Compared with ABG Analysis in Patients with Unilateral Lung Pathology

Patient no. (FI_{O_2})	Diseased lung dependent		Good lung dependent	
	SaO_2 by oximeter	$\text{SaO}_2/\text{PaO}_2$ by ABG	SaO_2 via oximeter	$\text{SaO}_2/\text{PaO}_2$ via ABG
1 (0.5)	84	87/62	98	99/110
2 (0.7)	80	82/57	95	95/84
3 (1.0)	72	70/43	93	92/76
4 (0.6)	90	90/64	99	98/98
5 (1.0)	73	74/50	91	90/63

to be discovered and more appropriate changes in therapy to be instituted (e.g., limiting the tilting of the Rotabed so the diseased lung does not become dependent, nursing the patient with the good lung dependent, or PEEP applied to the diseased lung only). Continuous pulse oximetry guided therapy in these patients when single ABG analysis may have been misleading.

Monitoring with continuous pulse oximetry allows the physician noninvasively to monitor changes in oxygenation (reflected in SaO_2) dependent on patient position in patients with unilateral lung disease as they are rotated on a Rotabed.

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Book Reviews

Neurosurgical Anaesthesia and Intensive Care, 2nd Edition.

T. Victor Campkin and John Morris Turner. London: Butterworth, 1986, 323 pp, \$39.85.

This book represents an update to the first edition originally published in 1980. In the preface the authors state that their goals were to outline basic neurophysiologic and neuropathologic principles and to describe anesthetic techniques to serve as guidelines for the safe practice of neuroanesthesia. In this they succeeded. For this edition, they have extracted from the recent literature relating to brain function, ICP, and the effects of anesthesia on the intracranial contents only that which is currently important to the practice of neuroanesthesia. In addition, changes have been made to reflect current anesthetic practice. For example, the chapter on induced hypothermia (a technique rarely used today) has been condensed to a short section, whereas other sections have been added. These include concise sections on the pathophysiology of cerebral ischemia and the pharmacologic therapy for cerebral ischemia; an expanded section on spinal trauma; several sections on electrophysiologic monitoring: EEG, processed EEG, and somatosensory evoked potentials. The sections on anesthetic action have also been updated with emphasis on the use of isoflurane and newer intravenous agents.

As in the first edition, the book is divided into four sections. The first, entitled "Physiology and Pharmacology," describes the cerebral circulation: blood flow and metabolism, intracranial pressure, and the intracranial effects of anesthetic agents. The chapter on the cerebral circulation is the least detailed. For the sake of brevity, information has been included without reference and without further explanation, making some statements confusing. The subsequent chapters in this section are well written and adequately detailed.

Part Two describes basic considerations for neuroanesthesia, including techniques for induced hypotension and for reducing intracranial pressure. There are detailed descriptions of neuroanesthetic techniques used in the United Kingdom. My only objection to this section is the description of the use of spontaneous ventilation during neurosurgery for the detection of brain stem ischemia. The risks of hypoventilation leading to hypercarbia and hypoxia and the resultant changes in cerebral blood flow and ICP out-

weigh this benefit and, at least in the United States it is common practice to use controlled ventilation during all neurosurgical procedures.

Part Three, entitled "Clinical Neuroanesthesia," provides an excellent overview of neuropathology and description of neurosurgical procedures. Detailed descriptions of anesthetic techniques specific to the surgical procedure are provided. These, together with the basic neuroanesthetic techniques described in Part Two, should prove very useful for residents and anesthesiologists unaccustomed to providing anesthesia for neurosurgical procedures.

Part Four provides a brief description of postoperative intensive care and care for the head-injured patient including the assessment of neurologic function and the application of the principles of neurophysiology and neuropharmacology used intraoperatively into the postoperative period.

The book is clearly written and the second edition is set with larger print than the first edition and has section titles in bold face that make it easy to read. Unfortunately, there were several typographical errors, including errors in names and dates in references that should have been corrected. The most obvious of these describes hypoxemia as $\text{PaCO}_2 < 10 \text{ kPa}$.

This book will provide useful information to anesthesia residents and clinicians wishing to learn more about neuroanesthesia, and should be included in every anesthesia department library.

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Drugs in Anaesthesia: Mechanisms of Action

S.A. Feldman, C.F. Scurr, and William Paton. London: Edward Arnold, 1987, 456 pp, \$79.50.

I enjoyed reading this book. The editors state in their preface that this textbook is not intended to be a text of pharmacology, but rather a framework of basic scientific data and principles of mechanisms of drug action which will allow an assessment of the specific attributes of new drugs

that are rapidly being produced. This book is not a standard basic pharmacology text for the anesthesia resident, but a book to be "dipped into" and used as a valuable reference source. However, it will be a suitable text for the anesthesiology "fellow" and anesthesiologist with a particular interest in anesthetic pharmacology.

The book is divided into three parts. Part One describes the general principles of pharmacology, such as pharmacokinetics and receptors; Part Two, the specific mechanisms of action of all the typical drug classes, such as hypnotics, general anesthetics, neuromuscular blocking agents, local anesthetics, and opiates; Part Three has four useful appendices that present the mechanisms by which drug interactions, side effects and toxicity occur, together with methods of drug analysis and delivery. The editors have gathered together a group of authors who are all international experts and well qualified to write on their particular topics. The book focuses on mechanisms of drug action at a basic level rather than describing in general terms the pharmacology of each drug. It is a well written and interesting contribution to anesthetic pharmacology and would be an excellent addition to all anesthetic departmental libraries.

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Anesthesia and Transplantation Surgery: Contemporary Anesthesia Practice

Burnell R. Brown Jr, ed. Philadelphia: FA Davis, 1987, 257 pp, \$35.00.

Anesthesia for organ transplantation is now coming to the forefront of our practice. As the years go by, more and more transplantations of body organs will take place and, as additional medical personnel become trained, scientific advances are made in preservation and immunology, and public awareness increases, the demand for transplantation procedures will continue to rise.

This issue of *Contemporary Anesthesia Practice* is dedicated to anesthetic considerations for various types of transplantation surgery. The content of the book concerns the medicolegal aspects of transplantation, organ procurement considerations, and heart, heart-lung, liver, and renal transplantation.

The chapters vary in scope of coverage. For instance, the chapter on forensic and medicolegal aspects of transplantation contains a detailed discussion of medicolegal problems encountered in transplantation. Although slanted toward heart transplantation, it is liberally spattered with direct quotes from the legal literature (30% of the chapter). Topics covered are the Uniform Anatomical Gift Act, sale of organs, jurisdictional disputes, recipient selection, and informed consent. Most of the chapters on cardiac transplantation deal with the University of Arizona Health Sciences Center experience and a description of their protocols.

Anesthesia for orthotopic liver transplantation (OLT) is divided into pediatric and adult management. The authors describe considerations to be taken into account preoperatively and intraoperatively which are backed up by data from their clinical experience. An important discussion missing from this chapter, though, is the diagnosis and treatment of intraoperative coagulopathies which are frequently encountered during OLT.

An interesting chapter dealt with considerations for the total artificial heart. It went into the history behind the device and the physiologic considerations. This was followed by case discussions and recommendations for anesthesia. The authors presented a concise discussion with liberal use of charts, graphs, and figures to expand on the topic.

This book is not intended to be an all-inclusive review of anesthesia for organ transplantation, but rather a brief overview of selected transplantation procedures and associated issues. The authors have accomplished this goal by relying on their clinical experience and providing pertinent references. The bulk of the emphasis is on the management of the various aspects of cardiac transplantation and offers a succinct summary for anyone specifically interested in this topic and organ transplantation in general.

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Anesthesia and Organ Transplantation

Simon Gelman, ed. Philadelphia: WB Saunders, 1987, 254 pp, \$49.95.

This multiauthored text is primarily intended for anesthesiologists dealing with the intraoperative care of patients undergoing various organ transplantations. However, it is of broad scope and would be beneficial reading for individuals desiring insight into the intraoperative management of organ transplantation.

The text is well organized, and each chapter is its own entity containing essential information so that overlap is minimal. The book covers most of the field of transplantation by reviewing immunology, brain death and ethics, organ preservation, immunosuppressive therapy, infection, kidney, heart and heart-lung, liver and skin transplantation, reimplantation of severed limbs, and blood transfusion. The authors were well chosen for their areas of expertise. Doctors Kang and Gelman particularly have used their vast experience in the field of liver transplantation and liver physiology to provide the reader with an in-depth review of the management of this group of patients. The only areas not covered are corneal, pancreatic, and intestinal transplantation, but as pointed out in the preface, there is a paucity of information in the literature concerning these procedures. Because of the format, this book can be

read cover to cover for a broad overview or on a chapter by chapter basis to study a specific area.

There is also uniformity to the organization within each chapter. The chapters that deal with organ transplantation (kidney, heart and heart-lung, liver, and skin) are remarkable for their concise but complete coverage of the topic. These chapters are replete with pearls of information that will help the anesthesiologist chip away at the many patient variables. Topics covered (where pertinent) are: anatomy and physiology, history of the technique, donor procedures, surgical technique, and anesthetic management including pre-, intra-, and postoperative considerations. Also noteworthy is that differing points of view are described. There is an adequate proportion of illustrations and charts to aid in understanding the text. On a whole, the illustrations are well labeled, but in a few instances there are some with no descriptions. The wealth of information is well documented in the bibliography in all but one chapter. As one who likes to refer to references during reading, I found the lack of statement documentation in this one chapter disturbing.

There is now an increasing public acceptance of organ transplantation as evidenced by numerous press reports. As was so aptly pointed out in the text, we are only seeing the tip of the iceberg in the sciences of immunology and organ preservation. As further advances are made and public demand increases, we, as a profession, are going to be confronted more often with patients who require organ transplantation and transplanted patients returning to the operating room for subsequent procedures.

For anyone who is involved in a transplantation program or desires to learn more about this area, this text is enjoyable to read, concise, and very highly recommended.

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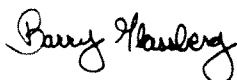
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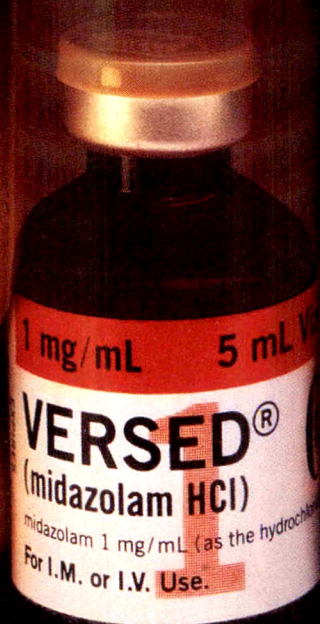
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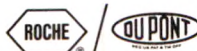
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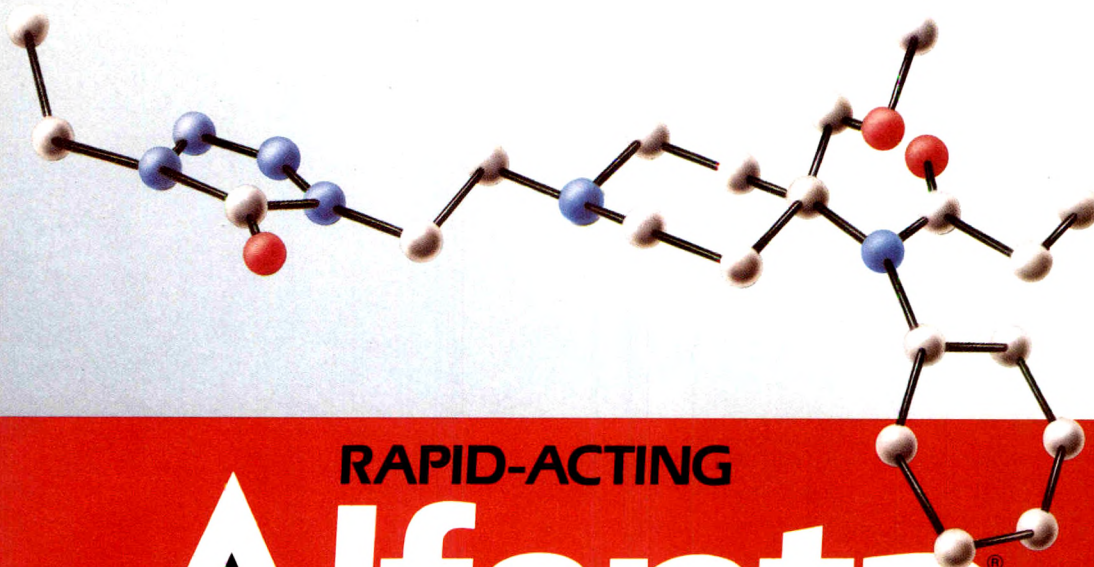
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(alfentanil HCl) Injection **Ⓢ**

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for short procedures lasting up to 30 minutes
in spontaneously breathing patients, or for procedures
lasting 30 to 60 minutes in intubated patients

CONTINUOUS INFUSION

for procedures lasting more than 45 minutes
in intubated patients

*As with other opioids, hypotension and bradycardia have been reported.

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

See following page for brief summary of Prescribing Information.

RAPID-ACTING

Alfenta®

(alfentanil HCl) Injection

AN OPTIMAL OPIOID ANESTHETIC FOR MOMENT-TO-MOMENT CONTROL

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION, OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg, following loss of consciousness; a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO₂. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported, therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and non-disturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N=785) %	Fentanyl (N=243) %	Thiopental Sodium (N=66) %	Enflurane (N=55) %	Halothane (N=18) %	Saline Placebo* (N=18) %
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate/nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD₅₀ of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSEAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

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U.S. Patent No. 4,167,574
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INDIANA

Faculty positions are available at the Assistant and Associate Professor levels. All candidates for these positions must be in the examination system or board certified. Please send a curriculum vitae to Robert K. Stoelting, M.D., Professor and Chairman, Department of Anesthesia, Fesler Hall Room 204, 1120 South Drive, Indiana University School of Medicine, Indianapolis, IN 46223.

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UNIVERSITY OF MISSOURI

Anesthesiologists needed at Assistant and Associate Professor levels. Must be Board certified or Board eligible. Duties include patient care, resident and medical student teaching, and research. Positions available at the University of Missouri Health Sciences Center. Interested applicants send a Curriculum Vitae to: G. W. N. Eggers JR,

MD, Professor and Chairman, Department of Anesthesiology, University of Missouri-Columbia Health Sciences Center, Columbia, MO 65212.

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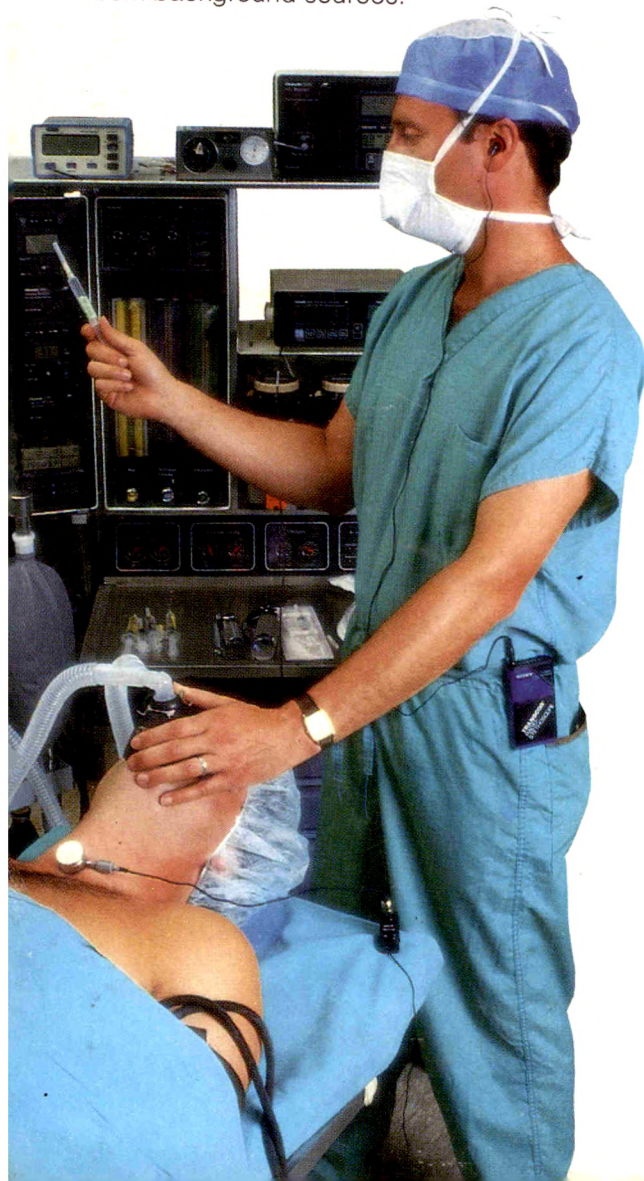
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